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Department of Health, Education, and Welfare

Food and Drug Administration

Diethylstilbestrol; Withdrawal of Approval of New Animal Drug Applications; Commissioner's Decision

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. 76N-0002]

Diethylstilbestrol; Withdrawal of Approval of New Animal Drug Applications; Commissioner's Decision

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The agency is publishing the Commissioner of Food and Drugs' decision, which constitutes his findings of fact and conclusions of law on the issues in a formal evidentiary public hearing, withdrawing approval of new animal drug applications for diethylstilbestrol implants and liquid and dry feed premixes for use in cattle and sheep.

EFFECTIVE DATE: June 29, 1979.

ADDRESS: The transcript of hearing, evidence submitted and all other documents cited in the decision may be seen in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, from 9 a.m. to 4 p.m. Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Constantine Zervos, Scientific Liaison and Intelligence Staff (HFY-31), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4490.

SUPPLEMENTARY INFORMATION: Although this document contains minor editorial changes from the original decision, such changes are made only to comply with document drafting guidelines issued by the office of the **Federal Register**; there are no substantive differences between the document that follows and the official copy of the Commissioner's Decision dated June 29, 1979.

The Commissioner's Decision

As Commissioner of Food and Drugs, I am, pursuant to 21 U.S.C. 360b(e)(1) and the authority delegated to me in 21 CFR 5.1(a)(1), ordering withdrawal of approval of new animal drug applications (NADA's): 10421, 10964, 11295, 11485, 12553, 15274, 31446, 34916, 44344, 45981, and 45982. These NADA's are for diethylstilbestrol (DES) implants and liquid and dry feed premixes for use in cattle and sheep. This action is taken on the basis of the record developed at an administrative hearing held pursuant to 21 U.S.C. 360b(e).

On this day I have also issued an order revoking 21 CFR 556.190. That regulation identified the mouse uterine/paper chromatography method of analysis as the approved method for determining whether DES residues exist in edible tissues of cattle and sheep treated with DES. As discussed below, the adequacy of that or any other method for detecting DES residues was an issue in the evidentiary hearing on the withdrawal of approval of the DES NADA's. The order revoking 21 CFR 556.190 states that nothing in the record of the evidentiary hearing demonstrates that the agency's previously announced decision to revoke that regulation is incorrect. My analysis of the evidence in this record on that issue is contained in this Decision.

The Initial Decision of the Administrative Law Judge who presided at the evidentiary hearing on the withdrawal of the DES NADA's was issued on September 21, 1978. All parites filed exceptions to that decision pursuant to 21 CFR 12.125(a). My decision accords with the Initial Decision insofar as the Administrative Law Judge found that approval of the NADA's must be withdrawn pursuant to the so-called "safety clause" of 21 U.S.C. 360(e)(1)(B) (discussed below). The Administrative Law Judge also found that the Delaney Clause (also discussed below) did not apply to DES because no DES residues have been found in edible tissues by the approved analytical method. I do not reach that issue because I find that the Delaney Clause applies to DES by virtue of the revocation this day of 21 CFR 556.190.

The applicants who sought a hearing on the withdrawal of the DES NADA's are American Home Products Corp., Dawes Laboratories, Inc., Hess & Clark, Division of Rhodia Inc., and Vineland Laboratories, Inc. They have filed joint papers and are referred to as the "manufacturing parties." Nonparty participants favoring continued approval of DES are the American Society of Animal Science, The Pacific Legal Foundation, and the National Cattleman's Association and are referred to as the "intervenors." The Bureau of Foods and the Bureau of Veterinary Medicine of the Food and Drug Administration (FDA) appeared jointly in favor of withdrawal and are referred to as the "Bureaus."

Testimony was submitted in written form, with an opportunity for oral corss-examination. Written testimony was given exhibit numbers. Citations to the record in this Decision are as follows: manufacturing parties' exhibits (M-); Bureaus' exhibits (G-); intervenors' exhibits (PA-, PN-, PP-, PS-,); transcript of cross-examination (Tr. at); entries in administrative (but not evidentiary) record (Record No.); Initial Decision (I.D. at). I also cite to the parties' exceptions. Because the Bureaus' arguments are most fully explained in their brief to the Administrative Law Judge, I sometimes refer to that document.

The manufacturing parties have requested oral argument (Manufacturing Parties' Exceptions at 11). Because I do not find oral argument necessary, I am denying that request, cf. 21 CFR 12.125(e).

This Decision constitutes my findings of fact and conclusions of law on the issues in this hearing and supersedes the initial decision. The statement of the history of this proceeding set out below is, however, taken with only slight modification directly from the Initial Decision.

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I. Introduction

(A) Diethylstilbestrol

DES is one of a class of chemicals known as stilbenes. Stilbenes are not produced metabolically by animals; DES does, however, produce effects similar to those produced by endogenous estrogens (G–189 at 2).

DES is used as a growth promotant in cattle and sheep. It is approved for use as an additive to animal feed, 21 CFR 558.225, and as a subcutaneous ear implant, 21 CFR 522.640. (It is implanted as a pellet of DES, which dissolves over time and thereby provides DES continuously to the animal's circulation.)

DES is a carcinogen in animals. See section II below. This fact has been noted by two different Courts of Appeals, See *Hess & Clark, Division of Rhodia, Inc.*, v. *FDA*, 495 F.2d. 975, 979 (D.C. Cir. 1974); *Chemetron Corp.* v. *U.S. DHEW*, 95 F.2d, 995, 997 (D.C. Cir. 1974); *Bell* v. *Goddard*, 366 F.2d. 177, 179 (7th Cir. 1966). The "DES exception" to the Delaney Clause, discussed below, was written precisely because the Congress understood that DES is a carcinogen in animals. See, e.g., 108 Cong. Rec. 21077–83 (1962).

One of the issues in the hearing is stated as follows: "Is DES a carcinogen, and is there a known no-effect level for its carcinogenic properties?" (I.D. at 2). The manufacturing parties do not argue that DES is not a carcinogen (though they never concede that it is). Rather, they argue that "there is a no-effect level below which DES is not associated with carcinogenesis" (Manufacturing Parties' Narrative Statement at 1, Record No. 76). In any case, manufacturing parties' witnesses have stated that DES is a carcinogen, though they argue it is only as carcinogenic as endogenous estrogens (see Manufacturing Parties' Exceptions at 96–97).

The record shows that animal drug use of DES is banned in Canada (M–51 at 29) and in many European countries (M–64 at 24 G–84 at 59). DES was once used as an implant in poultry, but approval of that use has been withdrawn, see *Bell* v. *Goddard, supra.*

(B) History

The use of DES in feed premixes was first approved in 1954 under section 505 of the Federal Food, Drug, and Cosmetic Act. The approval was based on data that demonstrated that, using the mouse uterine test, no residues could be detected in edible tissue of livestock 48 hours after withdrawal.

Approval for DES implants in cattle also became effective in 1955 on the basis of mouse uterine assay data demonstrating "no residue" under the permitted conditions of use. Applications became effective for DES in sheep feed premixes and implants in 1957 and 1959, respectively.

The current standards for approval of NADA's are set forth in 21 U.S.C. 360b. 21 U.S.C. 360b(d)(1)(H) imposes additional restrictions on the approval of animal drugs that have been shown to cause cancer. Under that section, no drug may be found to be safe if:

> * * * such drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal,* * *.

This language is the codification in 21 U.S.C. 360b of the anticancer clause that was added to the Federal Food, Drug, and Cosmetic Act by the Food Additives Amendment of 1958. This language is referred to as the "Delaney Clause."

In 1962, Congress amended the Delaney Clause to permit approval of a carcinogen as an animal drug in certain circumstances. As it appears in the present new animal drug provision, the added language is as follows (21 U.S.C. 360b(d)(1)(H)):

> [The Delaney Clause] shall not apply with respect to [a drug that causes cancer] if the Secretary finds that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice (i) such drug will not adversely affect the animals for which it is intended, and (ii) no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (c), (d), and (h) [of this section]), in any edible portion of such animals after slaughter or in any foods yielded by or derived from the living animals;* * *

This amendment became known as the "DES exception" because it was enacted with the DES situation in mind. See, e.g., 108 Cong. Rec. 19916–19920 (Sept. 27, 1962). (It has also been referred to as the "DES clause" or the "DES proviso.") In accordance with this amendment, FDA in 1963 issued food additive regulations providing for the use of DES in animal feeds and establishing official methods for detection, identification and measurement of DES residues (28 FR 1507; Feb. 16, 1963).

The official assay method is composed of the mouse uterine assay, which measures total estrogenic activity at 2 parts per billion (ppb), and the paper chromatography assay, which was thought to be capable of differentiating DES from other estrogens at levels above 10 ppb, 21 CFR 556.190. These assays have been approved since 1963.

Since publication of the detection method in 1963, a number of NADA's for the use of DES have been approved by FDA (41 FR 1804; Jan. 12, 1976). In each instance, the agency concluded that if, when the drug was used in accordance with the conditions of use prescribed in the labeling, DES residues could not be detected in edible tissue by the approved method, the requirements of the law were satisfied (id.). As discussed in sections II(A) and III(B), new information about DES and a reevaluation of the data before the FDA at the time the method was approved have now placed this conclusion in question.

Radioactive tracer studies conducted by the United States Department of Agriculture (USDA) in the early 1970's suggested that use of DES under the prescribed conditions of use can result in residues in edible tissues (id.). These radioactive residues were found at levels that are below the sensitivity of

the officially recognized assay methods. (See section III(B)(2).)

On March 11, 1972, FDA published a notice of opportunity for hearing on the proposed withdrawal of approval of NADA's for DES premixes (37 FR 5264; March 11, 1972). On June 21, 1972 (37 FR 12251), a similar notice was issued for both DES premixes and implants under the same provision of the act. The notice stated that the hearing procedures were being invoked in order to develop on the public record the information necessary for a formal decision on DES.

On August 4, 1972 (37 FR 15747), hearings on DES liquid and dry feed premixes were denied on the ground that holders of NADA's failed to demonstrate the presence of genuine and substantial issues of fact. Approval of NADA's for DES premix was therefore withdrawn (37 FR 15749) pursuant to 21 U.S.C. 360b(d)(1)(H) and 360b(e)(1)(B). Final ruling on DES implants was deferred pending receipt of the results of a USDA study.

The USDA radioactive-tagged DES implant study showed the presence of DES residues 120 days after implantation. On the basis of this information, FDA withdrew approval of NADA's for DES implants on April 27, 1973 (38 FR 10485) under 21 U.S.C. 360b(e)(1)(B). The same order denied the requested hearings for lack of genuine issues of material fact.

The manufacturers petitioned for review of the above orders under 21 U.S.C. 360b(h). The United States Court of Appeals for the District of Columbia Circuit reversed FDA's actions on the procedural ground that it was necessary to hold a public hearing before final action could be taken. *Hess & Clark* v. *FDA, supra; Chemetron Corp. v. HEW, supra.* These decisions reinstated the regulations and approvals for DES NADA's.

On March 27, 1974 (39 FR 11299), the FDA proposed to revoke the approved method of analysis for DES (mouse uterine and paper chromatography) on the grounds that this method failed to meet the requirements of accuracy, sensitivity and specificity. On January 12, 1976 (41 FR 1804), the agency responded to the comments on this proposal. On that date it also issued the notice of opportunity for hearing that initiated the present proceeding. The FDA stated that it intended to revoke the methods regulation at the time that it took final action on the notice of opportunity for hearing.

The manufacturing parties requested a hearing and, on November 26, 1976 (41 FR 52105), FDA issued the notice of hearing for this proce

(C) Issues

The issues in this proceeding, as set forth at the February 14, 1977 Prehearing Conference and modified by Order of the Commissioner on March 23, 1977, are as follows (I.D. at 2–3):

(1) Is DES a carcinogen, and is there a known no-effect level for its carcinogenic properties?

(2) Does DES have any adverse biological effects other than carcinogenesis that call its safety into question under the previously approved conditions of use and have safe tolerance levels been established for those effects?

(3) Has the existence of residues in edible tissues resulting from the use of DES been sufficiently established to call its safety into question under the previously approved conditions of use?

(4) Have any residues resulting from the use of DES implants and DES in feed been detected in edible tissues of animals presented for slaughter and are such residues likely to occur when the approved conditions of use are followed?

(5) Are there adequate and reliable methods, that are practicable for regulatory purposes and capable of detecting and identifying residues in edible tissue resulting from the use of DES at all levels above the level taken as the operational definition of no residue, or at all levels above a level established as a safe tolerance for any noncarcinogenic adverse effects, whichever is lower?

(6) Can adequate and necessary conditions for safe use be established?

(7) Is the mouse uterine/paper chromotography mothod, which is the assay currently approved for DES by regulation, adequate and practicable for regulatory purposes and capable of detecting and identifying residues in edible tissues resulting from the use of DES?

(8) If substances resulting from the use of DES under the conditions of use on the basis of which the NADA's were approved present some potential hazard to the public health, do the public health, environmental and economic benefits from the continued use of DES as an animal growth promotant outweigh that potential hazard?

(9) Will the withdrawal from the market of DES for use as an animal growth promotant significantly affect the quality of the human environment?

(D) General Introductory Comments

This Decision is a legal document in which are resolved difficult scientific issues. A few introductory notes may be helpful in understanding the discussion that follows.

First, the Decision discusses what might at first appear to be very small amounts of DES in edible tissues of meat from treated animals. Yet, as a respected cancer expert has testified, we have no data upon which to base the conclusion that any amount of a carcinogen above the single-molecule level would not produce a response (Tr. at 266 (Dr. Shimkin)). (Two ppb DES in 100 grams (slightly less than a quarter of a pound) of liver means that there are 450 trillion molecules of DES in that piece of liver (G–72 at 3).) The risk of cancer would, of course, be expected to be lower the smaller the number of molecules of a carcinogen that are ingested (cf. Tr. at 266).

Second, this Decision draws conclusions from animal tests in which relatively small numbers of animals are fed relatively large amounts of DES. (As discussed below in section III(D)(2)(a) of this opinion, however, some witnesses testified that 6.25 ppb of DES caused mammary tumors in mice in the Gass study.) Because animal tests can of necessity use only a relatively small number of animals (compared to the total U.S. population that eats meat from animals treated with DES), it would take an extremely potent carcinogen to demonstrate a response in an animal test when a substance is administered at the dose level at which humans actually eat that substance. (See, generally, the discussion of this problem at 42 FR 19998 (Apr. 15, 1977).)

A number of considerations are involved in interpreting animal data, and I do not wish to oversimplify that task. But clearly, if one is concerned to detect a substance that, at the dose level at which it is actually consumed, will cause cancer in 1 in 10,000 individuals (about 22,000 cancers in the U.S. population), a test of that substance at that dose level in 100 (or even 1000) animals is not likely to be successful. Even with 10,000 or 100,000 animals, the number of "spontaneous" cancers is likely to obscure the effect of the substance that causes cancer at the rate of 1 in 10,000. For reasons of cost and general practicality, most animal cancer studies are limited to a couple of hundred individual animals per dose level. As explained at 42 FR 19998, scientists generally assume that for cancer and other toxic effects, the amount of an effect is a function of the size of the dose administered although there is controversy about effects of very low doses. For these reasons, it is necessary and appropriate to utilize results from higher dosages in small numbers of animals to compute risks from lower dosages in the human population unless there is some reason not to do so.

(As is discussed in section III(D)(1), the manufacturing parties argue that there are reasons for not making this extrapolation with DES. I explain in detail my reasons for rejecting those arguments at the point in the opinion at which the arguments are discussed.)

Third, the risk associated with DES must be considered in light of the widespread consumption of DES-treated meat. In 1975, over 25 million head of DES-treated cattle (and over 7 million head of DES-treated sheep) were reported slaughtered (G–68 at 3).

Fourth, although there is evidence, discussed below, that DES used as medication in pregnant women causes cancer in some of their female offspring, it is unlikely that any individual will ever be identified as having been afflicted with cancer because he or she consumed meat containing residues of DES in the range of parts per billion. As Dr. Saffiotti pointed out, because our population is inevitably exposed to a variety of carcinogens, it is generally impossible (in the absence of evidence of, for example, occupational exposure to carcinogenic chemicals) to attribute any specific cancer to any specific cause (G–80 at 6). Yet this record warrants a finding that a significant (though unquantifiable) number of the cancers that do occur in this country today are associated with the use of DES in food-producing animals.

II. The Delaney Clause

There is no dispute that DES is a carcinogen when ingested by animals (see discussion above; G–22; G–34 at 1; G–37 at 2; G–46 at 2; G–47; G–59 at 2; G–70 at 2; G–80 at 7–8; G–84; G–85 at 6). As noted above in section I(B), I may not approve (and must withdraw approval of) the NADA for any animal drug that induces cancer when ingested by animals unless that drug comes within the DES exception to the Delaney Clause, 21 U.S.C. 360b(e)(1)(B); (d)(1)(H). A drug comes within the DES exception only if it is found that (1) the animals treated with the drug will not be adversely affected by it and (2) no residue of the drug will be found, by methods prescribed or approved by the Commissioner by regulation, in the edible products of the treated animals, 21 U.S.C. 360b(d)(1)(H).

The Administrative Law Judge found that neither the approved analytical method for DES nor any other analytical method is adequate for use with DES (I.D. at 51). He was not, however, authorized to revoke the regulations setting out the approved analytical method for DES and did not purport to do so. Because, at the time of the Initial Decision, there was an approved method and no residues had been reported by that method, the Administrative Law Judge found that the Delaney Clause had not been shown to apply to DES (I.D. at 13).

For the reasons stated in the following section, I am now revoking the analytical method for DES. My decision to do so is supported by the evidence in the record, discussed in section II(A), that no analytical method is acceptable for DES. Because there is now no approved method of analysis for DES, I conclude that the Delaney Clause applies to the drug. I therefore withdraw approval of the DES NADA's on that ground.

The Bureaus filed exceptions to the Administrative Law Judge's ruling with respect to the Delaney Clause. They argue that, even if the methods regulation were not repealed, the record would nevertheless support withdrawal of approval pursuant to the Delaney Clause under two theories:

First, they argue that the record shows that DES causes adverse effects in cattle (Bureaus' Exception at 7ff). The question whether DES causes adverse effects in animals was not stated as an issue in this hearing, but some evidence that the drug does cause such adverse effects was elicited, primarily during cross-examination of an intervenor's witness (see Tr. at 2056–57; 2067; 2152).

Second, the Bureaus contend that the showing by other analytical methods that DES use causes residues above 2 ppb means that I cannot find that no residues "will be found" by the approved method (Bureaus' Exceptions at 3). Under this theory, the lowest level of detection of the approved method would become, in effect, a tolerance level, and a finding by another (unapproved) method that an animal drug caused residues above the tolerance level would be a basis for invoking the Delaney Clause.

Because I find that the revocation of the analytical methods regulation for DES requires invocation of the Delaney Clause with respect to the DES NADA's. I do not reach the issues raised by the Bureaus' exceptions.

(A) Revocation of the Analytical Method Regulation

(1) *Background.* The regulation prescribing analytical methodology necessary for invocation of the DES exception (21 CFR 556.190) may be revoked pursuant to the notice and comment procedures prescribed in the Administrative Procedure Act, 5 U.S.C. 553(c). Those regulations are specifically exempted by 21 U.S.C. 360b(d)(1)(H)(ii) from the additional requirements of subsections (c), (d), and (h) of 21 U.S.C. 360b.

The approved analytical method for DES residues comprises two independent measurements: measurement of the uterotrophic effect of DES in immature mice and measurement of the migration coefficient of DES by paper chromatography, 21 CFR 556.190. The most recent proposal to revoke the FDA regulation identifying this method as approved was published on March 27, 1974 (39 FR 11299). The proposal stated the agency's conclusion that the approved method was inadequate to satisfy the intent of 21 U.S.C. 360b(d)(1)(H) (the Delaney Clause) because its lowest limit of reliable measurement was not shown to be acceptable, and because there were unanswered questions about its specificity and accuracy. That proposal noted that the approved method was not being used by the Department of Agriculture in its monitoring program.

In the January 12, 1976 (41 FR 1804), notice of opportunity for hearing in this proceeding the FDA summarized, and responded to, the comments received in response to the March 27, 1974 proposal. That document stated that the method would be revoked at the time of final action on the notice of opportunity for hearing (41 FR 1807).

In announcing the decision to revoke the current regulations, the January 12, 1976 notice suggested that a replacement method might be approved if demonstrated to be adequate (id.). No potential replacement, however, is adequate. My analysis of the evidence in the record on this issue with respect to the approved method and the manufacturing parties' proposed replacement, the gas chromatography/mass spectrometry method, follows. (A second potential alternative method, the radio-immunoassay, is not sufficiently well developed for use (G–65 at 2; G–66 at 1–2) and is not relied upon by the manufacturing parties.)

(2) *Lack of Knowledge About Metabolism of DES.* For an NADA to be approvable pursuant to the DES exception to the Delaney Clause, that NADA must contain an analytical method that is capable of assuring that no drug residue of toxicological concern will appear in unsafe levels in edible tissues of treated animals (see G–72 at 7; G–57 at 2). For DES we do not know enough about the residues of toxicological concern to determine that any analytical method would satisfy this requirement.

Any substance that enters an animal body is metabolized (changed) by being broken down into smaller molecules, by binding to other molecules already present in the body, and/or by a combination of breaking down and binding. Therefore, it is expected (and in this case shown by data) that part of the DES administered to cattle and sheep is metabolized into other substances (see, e.g., G–72 at 6–7). Residues of DES in the

edible tissues of cattle and sheep will, therefore, be made up not only of DES itself but also of the metabolites of DES.

The record reveals no testing of the metabolites of DES that would provide a basis for determining which are the metabolites about which one should be concerned from the perspective of public health protection (cf. G–57 at 3). The record provides no data that would allow one to calculate at what level any metabolite that is a carcinogen might be regarded as safe. Even if we knew what the toxicologically important metabolites of DES were and what safe levels of those metabolites were, I could not find any analytical method acceptable on this record. The record provides no information about the rates of depletion of the different DES residues in cattle and sheep. Without that information, I could not determine whether DES itself or any other residue (i.e., a metabolite) of DES was the appropriate substance to be measured by an analytical method. (Generally, a method should detect one "marker" residue, whose absence, as determined by a method having a certain level of sensitivity, assures that the total residue will not be present above a safe level, computed for the total residue upon the basis of testing of its components; see G–24 at 10423 (44 FR 17070, 17095; March 20, 1979).)

As the Administrative Law Judge noted (I.D. at 41), Congress recognized that the safety of an animal drug to human consumers is dependent in part upon their consumption of that drug's metabolites ("any substance formed in or on food because of use of such drug"), 21 U.S.C. 360b(d)(2)(A). As noted, DES residues may include both DES itself and its metabolites. Without knowledge of (1) what the toxicologically important residues of DES are, (2) what levels of these residues may be considered safe, and (3) what the relationship of the various residues of DES to each other is, I cannot responsibly conclude that any analytical method for DES will provide assurance that edible tissues of treated animals will not be hazardous. (See G–72 at 6–7.)

(The manufacturing parties might argue that I do not need information about the metabolites of DES because the approved method would detect not only DES itself but also its metabolites that produce an estrogenic effect (cf. M–110 at 10). There are, however, a number of metabolites of DES that are not known to produce an estrogenic effect (see G–189 at 3–4). I discuss below, as part of the section (section III(D)(1) of this opinion) dealing with the so-called "safety clause," my reasons for rejecting the manufacturing parties' argument that one need be concerned only about the estrogenic effects of DES. Thus, I can not presume that no nonestrogenic metabolite of DES is of public health significance. I cannot, therefore, find that a method able to measure only estrogenic DES metabolites is acceptable.)

The lack of necessary information about the DES residues to be measured is itself a basis for revoking the currently approved analytical method and refusing to approve the gas chromatography/mass spectrometry method proffered by the manufacturing parties as an alternative. Moreover, there are serious faults with each of these methods, which would make them unusable even assuming that DES itself were the only DES residue of concern.

(3) *Inadequacy of the Approved and the Proposed Alternative Method.* The lack of a showing that either the approved analytical method or the gas chromotography/mass spectrometry method detects DES residues at a level low enough so that those residues do not pose a significant risk of cancer is the most important failing of the methods. Each of the deficiencies discussed, however, (except for the deficiency in the approved method with respect to the attribute of specificity) is an independent basis for disapproval of these methods.

(a) *Inadequacy of Approved Analytical Method.* The record in this case supports the FDA's previous decision that the regulation setting out the mouse uterine/paper chromatography method as approved must be revoked. The attributes upon the basis of which a method of analysis is judged include accuracy, dependability, lowest limit of reliable measurement, practicality and specificity (G–26 at 1–2; G–72 at 2, 9–10). For a method to be approved or remain approved by the FDA, each of the method's attributes must be adequate for regulatory purposes.

(i) *Accuracy and Dependability.* The mouse uterine assay requires that the uterine weight of mice fed the liver to be tested be compared to the uterine weight of mice fed control tissues. The proposal to revoke the regulation approving the method noted the possibility that estrogenic substances in the control tissues might cause DES in the tested tissues to go unnoticed. Therefore, a question was raised about the accuracy of the method (39 FR 11300). At the hearing, Bureaus' witness Dr. Rodricks stated his opinion that this method had not been shown to be accurate, but he did not explain the reasons for this statement (G–72 at 9–10).

FDA did not rely upon the lack of accuracy of the approved method in the 1976 decision to revoke the regulations. I do not, on the basis of this record, now rely on the alleged inadequacy of the method with respect to that attribute.

The Bureaus offered no evidence (other than the unexplained opinion of Dr. Rodricks (id.)) that the mouse uterine/paper chromatography method is not dependable. The Bureaus did argue that certain problems—namely, technical and environmental controls and performance time—may affect dependability and accuracy. These problems, however, are matters of practicality and are treated below under the discussion of that attribute. Thus, I do not find the approved method inadequate with respect to the attributes of dependability and accuracy. The mouse uterine/paper chromatography method, however, has been shown to be unacceptable for regulatory purposes with respect to the remaining three attributes.

(ii) *Lowest Limit of Measurement.* The prime attribute of a method, the lowest limit of reliable measurement, is the level (or amount) of the chemical under analysis below which the assay will yield no interpretable results (G–72 at 2). The mouse uterine assay can consistently measure estrogenic activity at the levels of 2 ppb DES equivalents (G–67 at 2; G–72 at 2–3; M–62 at 1; see also M–153 at 1; M–170 at 2). It does not, however, distinguish DES from other estrogens (G–67 at 3; M–62 at 1).

Paper chromatography is used with the mouse uterine assay in an attempt to provide the requisite specificity. Paper chromatography is alleged to be able to distinguish DES from other estrogens at levels equal to, or greater than, 10 ppb (G–72 at 10; cf. M–170 at 2). Assuming that this claim for the paper chromatography method is correct, the lowest level of reliable measurement of the approved method is effectively 10 ppb DES in liver tissues.

The manufacturing parties argue that 2 ppb should be accepted as the lowest limit of reliable measurement of the approved method. They argue, in effect, that if no residue is detected by the mouse uterine assay, one can be assured that no residue of 2 ppb DES or above exists. If a residue is detected by the mouse uterine assay, on the other hand, they argue that "additional samples of tissue can be analyzed by a variety of more specific techniques, such as gas liquid chromatography with mass spectrographic analysis" (M–110 at 11; Manufacturing Parties' Exceptions at 193). This argument, rather than

supporting the current method, in fact suggests that a new combination of assays should be substituted for those currently approved.

In any case, whether the lowest limit of the approved method is 2 ppb or 10 ppb, that limit is not acceptable because there is no basis for concluding that residues below either of those levels will not cause cancer in human consumers. (As the Administrative Law Judge noted, each of these limits is very close to the 6.25 ppb dosage that was reported to have resulted in a carcinogenic effect in the Gass mouse study (G–22) see section III(D)(2)(a)).)

My conclusion that no no-effect level has been shown for the carcinogenic effects of DES is discussed in detail below in section III(D)(2). Bureaus' witnesses Dr. Gross and Dr. Rodricks did calculate, using the Gass study (G–22) data, that no more than 1 part per trillion (ppt) of DES in the diet would be consistent with a risk of 1 cancer in one million consumers (a cancer rate assumed to be "acceptable" or "insignificant" or tantamount to no cancer) (G–34 at 2; G–72 at 4). (Another witness, Dr. Condon, had calculated the same figure from the Gass data, but did not purport to apply it to human beings (G–21 at 3).) Neither the approved analytical method nor any other method known to me is capable of measuring DES at the 1 ppt level.

Dr. Gross' testimony suggests, but, read carefully, does not state, that his calculation accorded with the regulations published by FDA to describe the agency's requirements for analytical methods under the DES exception (see G–24). That regulation has been invalidated on procedural grounds, *Animal Health Institute* v. *FDA*, Civil No. 77–806 (D.D.C. Feb. 8, 1978) and reproposed in a somewhat modified form (44 FR 17070; March 20, 1979). I do not, in this Decision, rely on either the invalidated regulation or the proposal. It must be noted, however, that the 1 ppt calculation of Dr. Gross and Dr. Rodricks neither accords with the procedure set out in the regulation nor represents an appropriately conservative calculation of a "safe" level for DES (cf. Tr. at 1082).

As discussed in section II(A)(2), DES residues in meat can be expected to be made up not only of DES but also of various metabolites of that substance. The computation of a "safe" level of DES must therefore be based upon the results of animal testing not only of DES but also of the metabolites of DES that appear suspect (cf. G–72 at 10). If steers transform DES into a metabolite that is not produced when DES is fed to mice and that metabolite is more carcinogenic than DES itself, calculations from the Gass mouse data will provide a "safe" dose that is too high.

The criticisms of the Bureaus' witnesses' calculations of a 1 ppt "no residue" level for DES set out above show only that that calculation is not sufficiently conservative. Testing of DES metabolites might produce a lower "no residue" level for the totality of DES and its metabolites but would not produce a higher one.

The manufacturing parties, however, argue that the procedure utilized in calculating the 1 ppt figure is totally invalid from a completely different perspective. They rely on the testimony of their witness, Dr. Weaver, and upon various internal FDA memoranda to support their criticisms of the method of calculation used. They argue that that method is based upon unduly conservative assumptions and has not been shown to provide consistent results when the same data are utilized as a basis for calculation (Manufacturing Parties' Exceptions at 195–204). They also argue that the Bureaus' witnesses used the wrong data as a basis for their conclusion. They contend that a proper calculation would (1) be based upon all data in the Gass study, (2) ignore the 6.25 ppb result, and (3) incorporate results from the uncompleted NCTR study (discussed in section III(D)(2)(a) of this Decision) (id. at 204–06).

The FDA, as noted above, had issued a regulation that relied upon the method of calculation purported to have been used by Drs. Condon and Rodricks (but not by Dr. Gross (Tr. at 423) (G–24)). I decline to decide, on this record, whether the method utilized (the modified "Mantel-Bryan technique") is appropriate for use—or was applied correctly here—because, for the reasons stated above, I find 1 ppt calculation unusable in any event and I do not rely on it.

The decision not to rely upon the 1 ppt figure avails the manufacturing parties not at all, however. My criticism of the Bureaus' 1 ppt calculation applies with equal force to the manufacturing parties' alternative calculation; they, too, ignore the issue of DES metabolites. I am left, therefore, with the conclusion that no no-effect level or acceptable level of risk has been shown for DES. The record does not allow me to determine what level of DES might be low enough to cause less than one cancer in one million persons (assuming that that level may be equated to "no residue"). The record provides no basis for concluding that that level is not well below the 2 ppb that the manufacturing parties have claimed as the lowest level of measurement for the approved method.

My rejection of 2 ppb as an adequate lowest limit of measurement does not reflect any "never-ending search for more and more delicate methods of analysis" (see Manufacturing Parties' Exceptions at 28). Rather, it reflects a "rule of reason" (id.), which embodies the basic principle that a method of analysis should have a lowest limit of measurement that is low enough to protect the public from cancer caused by an animal drug. My dissatisfaction with the limit of 2 ppb is based on the evidence of record that DES is an animal carcinogen and the lack of information sufficient to show that DES and its metabolites, when present at the level just below 2 ppb, are safe or present an acceptable risk.

(iii) *Practicality.* The manufacturing parties argue that practicality is not an attribute necessary for approval of an analytical method for purposes of the DES exception to the Delaney Clause (Manufacturing Parties' Exceptions at 210). They base their argument on statements made by former FDA chief counsel Peter Hutt before a Congressional committee (id.). Contrary to the manufacturing parties' position, however, Mr. Hutt did not say that an approved method need not be sufficiently practical for regulatory purposes. Rather, he said that a method need not be approved to be used for regulatory purposes. Hearing before the Health Subcommittee of the Senate Labor and Public Welfare Comm. on S. 2818, 92d Cong., 2d Sess. 41 (1972). More importantly, as a matter of common sense, I can not find that no residues of a drug will be found in edible tissues of treated animals by an analytical method if that method is not practical enough to be used to analyze such tissues in the normal course of business.

The mouse uterine/paper chromatography method is not practical for regulatory purposes. As the record shows, it takes over 2 weeks to perform the assay (G–26 at 2–3; G–67 at 3; M–170 at 2). The meat of animals whose livers were examined would normally have moved to market in a 2-week period (G–26 at 3). One manufacturing parties' witness did testify on cross-examination that he performed the assay in 9 days (Tr. at 1846). The fact that one laboratory can perform the assay in 9 days does not mean that regulatory laboratories carrying on a variety of work can consistently perform it in that period. Moreover, even if the assay could be completed consistently within 9 days, that length of time would

constitute an unacceptable delay in the regulatory process.

The evidence also revealed that the mouse uterine/paper chromatography method is technically difficult to perform (G–67 at 3). A large number of mice are required (Tr. at 514), and their environment—including cages and feed—must be carefully controlled (G–67 at 3). Neither the quantity of animals nor the technical expertise necessary for use of this method are generally available in government regulatory monitoring laboratories (G–26 at 3). The United States Department of Agriculture has determined that the method is not practical for regulatory use (Tr. at 487). I reach the same conclusion.

(iv) *Specificity.* Specificity is one of the cardinal attributes of a regulatory method. The method should respond monotonically to (i.e., show a continuously increasing response to) increasing concentrations of the substance measured (DES) and that substance only. My analysis of the evidence on the issue reveals a problem. The Bureaus did not provide expert testimony that the approved method is not sufficiently specific. Indeed, one Bureau witness stated that the paper chromatography assay provides the requisite specificity to the approved method (G–72 at 10). Yet, there is no objective evidence in the record—or elsewhere, as far as I know—that the approved method is sufficiently specific.

I conclude that the approved methods are not adequately specific for use. I recognize that, because the Bureaus failed to advance this argument, it would be unfair to rely upon it as a basis for revoking the approved methods. There are, however, three other independent bases for my decision to revoke the approval of this method: (1) the fact that there has been no showing that this assay provides information about the levels in edible tissues of all of the metabolites of DES that potentially have a carcinogenic effect, (2) the failure of the method to measure DES residues at a level at which those residues are shown not to present a significant risk from cancer, and (3) the method's impracticability. For that reason, I reject the idea that I must either accept the consensus of testifying experts that the method is sufficiently specific or remand the issue for further consideration. I wish to make clear, however, that I do not rely on the following expression of my views on this subject as a basis for my rejection of the approved method.

The question that must be answered by an analytical method for DES is: "in this tissue, is there DES and, if so, how much?"

The first type of measurement of the approved method, i.e., measurement of uterotrophic effect in immature mice, can provide either one of two answers to this question:

> "There is no DES at levels at or above 2 ppb"; or alternately, "There are X DES equivalents (at or above 2 ppb) some of which *might* be DES."

(Measured residues are expressed as "DES equivalents" because the residue content of analyzed tissues is compared to known amounts of DES added to tissues fed to control mice.)

The record contains no information to show that an analyst finding X DES equivalents can say with some specific level of confidence, say 50 or 60 or 90, that no more (or less) than a fraction of those equivalents is indeed DES. Thus, the measurement of uterotrophic effects in immature mice is entirely nonspecific.

This is so even if it is *assumed* that increasing DES equivalents in the tissue will cause increasing responses, i.e., if monotonicity of response is assumed. It has not been demonstrated, however, that this method even produces a monotonic response. (It is conceivable and indeed, judging from the developers' description of this assay (G–68 at 811 and 812, Figure 3), likely that, at some level, an increase in DES could fail to increase uterine growth.)

Paper chromatography of tissue extracts was incorporated into the approved analytical method so that the analyst could ascertain what fraction, if any, of what might be DES is indeed DES. In general, chromatography of any kind is a non-specific method of analysis. This lack of specificity of chromatographic methods was alluded to by Dr. Abramson in his testimony (M–38) discussing gas liquid chromatography, one of the most specific chromatographic methods of today. Single run paper chromatography, one of the most primitive chromatographic methods, is less specific than gas chromatography. I can not agree that this assay is specific enough for the purposes at hand.

(b) *The Gas Chromatography/Mass Spectrometry Method.* The evidence that the gas chromatography and mass spectrometry assays when used together constitute a method that is accurate, dependable, and practical (M–38 at 15–18, M–128 at 8) is convincing and not seriously controverted by the Bureaus. Like the mouse uterine/paper chromatography method, however, the gas chromatography/mass spectrometry method is inadequate with respect to its lowest limit of reliable measurement and with respect to its specificity.

(i) *Lowest Limit of Reliable Measurement.* Expert testimony at trial firmly established that for regulatory purposes the lowest limit of reliable measurement is 2 ppb (M–38 at 17–18; M–93 at 2; M–128 at 8; M–164 at 1; Tr. at 1361). For the reasons discussed in detail in section II(A)(3)(a)(ii) above, that limit is not acceptable for approval of an analytical method for DES.

(ii) *Specificity.* Like the mouse uterine/paper chromatography method, the gas chromatography/mass spectrometry method is not adequately specific for regulatory purposes. The gas chromatography/mass spectrometry method upon which the expert testimony was based (known as the modified Donoho procedure) is described in M–39. This method provides for the selection of a single mass or ion for identification (M–39 at 521–22). Yet, as the manufacturing parties' Dr. Abramson testified, the identification of a single mass or ion does not allow definitive identification without a confirmatory step in which more than one ion must be monitored (M–38 at 13–14). Therefore, it appears that the method as described in M–39 is not sufficiently sensitive to determine identity reliably.

There is a direct relationship between the number of ions monitored and the lowest limit of reliable measurement in this method. Increasing the number of monitored ions yields a higher lowest limit of reliable measurement (see, e.g., M–38 at 19). Thus, achieving specificity with the gas chromatography/mass spectrometry method will yield a higher lowest limit of reliable measurement than the 2 ppb suggested by the experts.

(4) *Conclusion As to Analytical Methods.* For the foregoing reasons, I find that neither the approved method nor any other method is acceptable as an analytical method for DES for purposes of the DES exception to the Delaney Clause. As noted, by order issued today, I have revoked 21 CFR 556.190, the regulation approving the current analytical method for detection of residues of DES.

(B) Effect of Revoking Currently Approved Method for Testing Drug Residues in Edible Animal Tissues Without Implementation of Another Approved Method

An applicant for approval of an NADA for a carcinogenic drug must submit, as part of that NADA, an acceptable method of analysis to detect residues of the drug in edible products of the treated animal, 21 CFR 514.1(b)(7)(ii). The statutory provision describing the contents of an NADA is clear: it requires the submission of a

"description of practicable methods for determining the quantity, if any, of [the] drug in or on food, and any substance formed in or on food, because of its use * * *." 21 U.S.C. 360b(b)(7). In addition, as the legislative history of the DES exception (discussed below) shows, that provision contemplates that the applicant will have the responsibility for developing an analytical method for a carcinogenic drug. This has been the FDA's consistent interpretation of the new animal drug provision. (21 CFR 514.1(b)(7)(ii), promulgated on September 14, 1971 (36 FR 18375), was the first interpretation by regulation of the 1968 New Animal Drug Amendments.)

When an applicant for approval of an NADA for a carcinogen fails to submit an adequate analytical method to detect residues, it of course follows that no regulation setting out an approved analytical method will be promulgated for the applicant's drug. The agency then cannot find that no residue of the drug will be found by an approved method; the DES exception to the Delaney Clause can not be applied; the Delaney Clause does apply and the NADA may not be approved, 21 U.S.C. 360b(d)(1)(H).

If the Commissioner determines, based on new information together with previously available information, that the approved analtyical method for detecting residues of an animal drug is inadequate, it is his responsibility to revoke the regulation that sets out that method. 21 U.S.C. 360b(e)(1) then compels him to withdraw all NADA approvals that were based on compliance with that regulation because 21 U.S.C. 360b(d)(1)(H) (the Delaney Clause) becomes applicable to the drug.

The manufacturing parties argue that the DES exception remains in effect unless and until the FDA finds illegal residues, using an approved analytical method, in the edible tissues of animals. They contend that if there is no approved analytical method to measure residues, the Delaney Clause does not authorize withdrawal of NADA approvals, no matter how high the residue levels may be. The manufacturers claim support for their theory in the opinions in *Hess & Clark, supra*, and *Chemetron, supra*, the legislative history of 21 U.S.C. 360b(d)(1)(H), and statements made by FDA officials in 1972. In addition, they argue that withdrawal of approval of the DES NADA's due to revocation of the currently approved analytical method would constitute an administrative repeal of the DES exception and permit the Commissioner to expand the grounds for withdrawal of an approved NADA beyond those listed in 21 U.S.C. 360b(e)(1) (Manufacturing Parties' Exceptions at 27–32).

The manufacturing parties' reliance on the *Hess & Clark* and *Chemetron* opinions is misplaced. Neither opinion addresses the issue of the operation of 21 U.S.C. 360b(d)(1)(H) in the absence of regulations describing an approved method for determining whether drug residues exist inedible tissues. The court in *Chemetron* does state: "The 'DES' exception to the Delaney Clause, discussed above, continues effective unless the agency detects residues in a slaughtered animal while using an approved test method, "495 F.2d at 999. The context in which this statement is made, however, makes it clear that the court was not considering a situation in which no method was approved. Rather, the court was assumning the continued existence of an approved method.

The legislative history of the DES exception does not support the manufacturing parties' argument. The Delaney Clause was added to the Food Additives Amendment passed in 1958 (Pub. L. No. 85–929, 72 Stat. 1785). The Delaney Clause was then incorporated in the 1960 Color Additive Amendments (Pub. L. No. 86–618, 74 Stat. 399). The DES exception was first proposed during consideration of the Color Additive Amendments in 1960. See, e.g., H.R. Rept. No. 1761, 86th Cong., 2d Sess. 89 (1960). It finally was added to the Food additive and color additive provisions as part of the Drug Amendments of 1962 (Pub. L. No. 87–781, 76 Stat. 785). The 1968 New Animal Drugs Amendment (Pub. L. No. 90–399, 82 Stat. 343). consolidated the Food additive and new drug provisions that dealt with animal drugs and incorporated the Delaney Clause and DES exception from the food additive provision.

The legislative history does not contain any direct statements of how the Delaney Clause and DES exception should apply to a drug for which no analytical method is approved. That history does clearly support, however, two propositions, each of which is a basis for the agency's interpretation of the statute and its rejection of the manufacturing parties' contrary interpretation.

First, it is clear that the burden was placed upon the NADA applicant to develop an appropriate method of detection. In a letter submitted to the committee holding hearings on the DES exception as proposed in 1960, the Secretary of Health, Education and Welfare, stated:

[I]t should be clearly understood that the industry still would have the responsibility of developing adequate analytical methods for detecting residues and furnishing them to the government with a petition for the approval of an additive.

(Cited in Hearings of FDA "Study of the Delaney Clause and Other Anticancer Clauses" Before a Subcommittee of the Committee on Appropriations, 93rd Cong., 2d Sess. 203–04 (1974).) The manufacturing parties have cited nothing in the legislative history of the DES exception that conflicts with the Secretary's expressed understanding of that exception.

Congressional inquiries into the DES exception since its passage have also supported the agency's view that an applicant must produce an acceptable analytical method. See, e.g., H.R. Rept. No. 93–708, 93rd Cong., 1st Sess. (1973), at 17, 26–27.

This allocation of burden is consistent with the general scheme of all the premarketing clearance provisions of the Food, Drug, and Cosmetic Act—those covering food additives (21 U.S.C 348, adopted in 1958), color additives (21 U.S.C 376, adopted in 1960), human drugs (21 U.S.C 355, adopted in 1938 and amended in 1962) and animal drugs (21 U.S.C 360b, adopted in 1968). Under all of these provisions Congress has consistently required that the manufacturer or other sponsor seeking approval of a substance or a product satisfy the burden or proving every element necessary for approval. See 21 U.S.C 348(b); 355b(b); 360(b); 376(b). The present case merely illustrates this fundamental and broadly applicable principle of public health protection deeply embedded in the Federal Food, Drug, and Cosmetic Act. There is no reason to treat the requirement for an adequate analytical method for residues caused by a carcinogenic animal drug any differently than the requirement that a food additive or color additive or human drug be shown to be safe. Thus, it is the manufacturing parties' responsibility to develop an acceptable method, and it follows logically that, if there is no acceptable method, Congress did not intend the manufacturing parties to benefit from that fact.

Second, the legislative history illustrates Congress' understanding that the Delaney Clause would apply unless the Commissioner could make a finding that no residues will be found in the products of the treated animal. In responding to the argument that the DES exception would diminish the Delaney Clause's protection of the public health, Congressman Harris stated (108 Cong. Rec. 21081 (1962)):

This amendment places the resonsibility on the Secretary of Health, Education and Welfare *to make a positive finding* that under the conditions of use and feeding specified in the proposed labeling and reasonably certain to be followed in practice, the feed additive will not, first, affect the animal; and, second, *that no residue of the additive will be found* in any edible portion of the animal after slaughter (emphasis added).

As the manufacturing parties point out, Congressman Harris had earlier been assured that the DES exception provided "the authority for the Secretary to see that no residue of the additive shall be found" (id. at 21080).

Senator Kefauver, a sponsor of the Drug Amendments in the Senate, explained the DES exception as follows (108 Cong. Rec. 20869 (Oct. 3, 1962)):

The provision stipulates that the anti-cancer proviso of existing law shall not apply with respect to the use of a substance—for example, a veterinary drug—as an ingredient of feed for animals which are raised for food production if the *Secretary finds* * * * *that no residue of the additive will be found* after slaughter or in any food product of the living animal—such as milk or eggs (emphasis added).

Senator Humphrey, also a strong supporter of the Drug Amendments (108 Cong. Rec. 22053 (1962)), described the DES exception and then stated that it

preserv[es] in its full vigor the Consumer protection now afforded by [the Delaney Clause].

I reiterate—consumer protection is assured.

These quotations (particularly the first two) reinforce the conclusion that is already clear from the language of the statute: the operations of the DES exception depends on the Commissioner making a finding of no residue (by use of a method approved by regulation). The DES exception does not begin to operate without that prerequisite finding. Clearly excluded by the language and the legislative history is the manufacturing parties' interpretation that the exception can apply without the prerequisite finding and that the discovery of some residue is necessary to prevent or stop its operation. That interpretation is totally inconsistent with the explanations offered by Rep. Harris and Senator Kefauver and it certainly would not preserve consumer protection "in its full vigor" as stated by Senator Humphrey. Indeed, under the manufacturing parties' interpretation, any deficiencies in analytical methodology that prevented identification of residues in the range material to protection of public health would be at the expense of public health protection. That certainly is not what Congress intended.

The congressional understanding that the Secretary (or, by delegation, the Commissioner) could find that "no residues" would be found in edible tissues may have been based on an operational definition of the term "no residue" as equivalent to no residues above a level that can be considered virtually safe. FDA has interpreteed the DES Exception in this way (see, e.g., 44 FR 17070 (March 20, 1979); G–24). Another conceivable explanation, which I consider improbable, is that the Congress was less scientifically sophisticated and believed that it was possible for the Commissioner to find that absolutely no residues would exist in the edible tissues of treated animals.

In any case, there was, without question, a congressional concern that the Commissioner find that there are "no residues" in edible tissues and there was a belief on the part of the legislators that the DES exception did nothing to diminish the protection to the public health afforded by the Delaney Clause. It is hardly consistent with that congressional intent to urge that Congress meant the Delaney Clause to be inapplicable whenever no analytical method had been approved for a drug.

The manufacturing parties rely upon a statement by former FDA chief counsel Peter Hutt at a 1972 Congressional hearing. In the statment referred to, he defended the proposition that the Delaney Clause did not sanction withdrawal of approval of NADA's based on the finding of residues by unapproved methods, hearings on Regulation of Diethylstilbestrol Before the Intergovernmental Subcommittee of the House Government Operations Committee, 92d Cong., 2d Sess. 385 (1972). Mr. Hutt advocated his position forcefully and extemporaneously (at one point informing the Committee that Congress did not appreciate what it was doing in passing the DES exception (id. at 386)). His statements cannot fairly be taken out of context to bear upon a question—whether the Delaney Clause applies if there is no approved method for a drug—entirely different from the issue he was addressing.

To the extent that Mr. Hutt's comments may be read to suggest that the Clause does not apply when no method exists, I explicitly disavow them on behalf of the FDA. Such a reading would be inconsistent with the language, legislative history, and purpose of the statute and with the FDA policy that supports the proposed regulations setting requirements for analytical methods (44 FR 17070 (March 20, 1979), cf. G–24).

The maunfacturing parties also refer to a statement included in material forwarded by FDA to Senator Proxmire in 1972 (M–167 at 4191–92). This statement, that the Delaney Clause requires findings by the approved method, assumed, as did Mr. Hutt's statements, that an approved analytical method existed for the drug in question (there DES). That statement did not address the question of the applicability of that clause when there is no approved method.

The manufacturing parties' argument that withdrawal of an NADA on the basis of revocation of the methods regulation is an administrative repeal of the DES exception is without merit. As Commissioner, I may not, of course, simply ignore the DES exception to the Delaney Clause, nor may I act arbitrarily and capriciously when a method is submitted for approval. I must approve an analytical method if an appropriate one is presented. On the other hand, it is implicit in the statutory requirement that the Commissioner "prescribe or approve" the methods of analysis that he must evaluate the method submitted and refuse approval of that method if he finds it inadequate. In sum the withdrawal of approval of an NADA upon revocation of the analytical method upon which approval is based implements, rather than subverts, the statute, including the DES exception.

(c) *Conclusions As to Delaney Clause Issue.* For the reasons discussed in this section II, I find that (1) approved analytical method for detecting DES residues is inadequate and that (2) no alternative method is adequate for use as an analytical method to detect DES residues. I reject the manufacturing parties' argument that the DES exception to the Delaney Clause is applicable if there is no approved analytical method for DES residues. I conclude, therefore, that the revocation of 21 CFR 556.190 requires the withdrawal of approval of the DES NADA's pursuant to 21 U.S.C. 360b(e)(1)(B) and 360b(d)(1)(H).

III. The Safety Clause

(a) Burden of Proof

for purposes of convenience, I refer to that part of 21 U.S.C. 360b(e)(1)(B) that does not deal with the Delaney Clause as the "safety clause." The burden of proof in this proceeding on the safety clause issue is derived from the clause itself, which is as follows (21 U.S.C. 360b):

(e)(1) The [Commissioner] shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application filed pursuant to subsection (b) of this section with respect to any new animal drug if the [Commissioner]

finds * * * (b) that *new evidence* not contained in such application or not available to the [Commissioner] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, *evaluated together with the evidence available to the [Commissioner] when the application was approved, shows that such drug is not shown to be safe* for use under the conditions of use upon the basis of which the application was approved * * * (Emphasis added).

As is apparent from the italicized language, approval may be withdrawn pursuant to the "safety clause" if new evidence, evaluated together with previously existing evidence, shows the drug is not shown to be safe. As Congress was careful to make clear, "new evidence" includes any evidence not available at the time the application was approved, tests by new methods, and tests by methods not originally considered applicable.

There does not appear to be an issue about the "newness" of the evidence upon which the Bureaus rely. DES was first approved in 1954. The Gass study was published in 1964, and did not come to the attention of FDA until 1971 (see M–1). The evidence concerning DES residues was not available until the 1970's.

Because the Bureaus are the proponents of withdrawal, it is appropriate that they have the burden of proving that the first "showing" (i.e., a showing that the drug is no longer shown to be safe) has been made, see *Hess & Clark, Division of Rhodia, Inc.*, v. *FDA, supra*, 495 F. 2d at 992. The Bureaus did not dispute this point.

The controversy arises over what is sufficient to constitute the required showing. The manufacturing parties argue that the Bureaus' burden is, in effect, to show that use of the drug is unsafe. There is, however, a clear congressionally recognized difference between "unsafe" and "not shown to be safe." Indeed, the statute uses both terms and clearly distinguishes between them. Compare 21 U.S.C. 360b(e)(1)(A) with 21 U.S.C. 360b(e)(1)(B). The former paragraph requires a finding that a drug is "unsafe"; the latter, a finding that the drug is "not shown to be safe." If the two terms were the same, there would not be two subparagraphs.

The Court of Appeals in *Hess & Clark, Division of Rhodia, Inc.*, v. *FDA, supra*, 495 F. 2d at 993, focusing on the residue issue (discussed below in sections III (B) and (C) of this Decision), stated its view of the burden question:

> We think it implicit in the statute that when the FDA proposes to withdraw an approval because new evidence shows the drug leaves residues, it has an initial burden of coming forward with *some evidence of the relationship between the residue and safety* to warrant shifting to the manufacturer the burden of showing safety. This is at least the case where, as here, the residues are of unknown composition. (Emphasis added.)

It is, of course, not possible to write a formula, semantic or otherwise, that will tell the decisionmaker exactly how much evidence is required to show that a drug is no longer shown to be safe. The Administrative Law Judge's formulation is as good as any: "In other words, the Bureaus must provide a reasonable basis from which serious questions about the ultimate safety of DES and the residues that may result from its use may be inferred" (I.D. at 8). I adopt this statement of the burden of proof in this proceeding. Even if the Bureaus had the burden to show that the presently approved uses of DES were unsafe, however, I would have to find, on this record, that they have carried that burden.

(B) Evidence That DES Use Results in Residues in Edible Tissues

I have carefully considered whether the evidence in the record shows that use of DES as an animal drug results in DES residues in edible tissues. (Except where the context indicates otherwise, a reference to "DES residues" in this Decision refers to residues identifiable as DES and/or its conjugates.) I have found convincing evidence on this issue from two separate sets of data: the radiotracer studies discussed in subsection (2) below and the results of the Department of Agriculture manufacturing program discussed in subsection (3). Though each supports the other, I find that each of these sets of data provides an independent basis for the conclusion that animal drug use under each of the approved DES NADA's does result in residues of DES and/or its conjugates in the edible tissues of treated cattle. I rely solely upon the radiotracer studies for my conclusion that approved uses of DES result in DES residues in the edible tissues of sheep. (As is discussed in detail in section III(D) below, I also find that these resulting residues are harmful.)

The residues in the tissues of treated animals observed by both the radiotracer studies and the Department of Agriculture monitoring program are not surprising. Anything administered to an animal's system remains in that system in small amounts indefinitely (see, e.g., M–167 at 4191; G–2 at 1192). The amounts of those residues, however, generally decrease as the time following administration increases. (One can visualize this phenomenon as an asymptotic or "decay" curve (see G–24 at 10428).)

When the withdrawal period for oral DES was originally set at 7 days, that action was not based upon the belief that after 7 days no DES residues would exist in meat (see G–72 at 3). Rather, that withdrawal period was set because at that point on the curve almost all residues would be below 2 ppb, which was once thought to be the safe dose for DES. It would be expected that the 7-day withdrawal period would result in residues in the 0.5 to 2 ppb range. Even a 14-day withdrawal period would reasonably be expected to result in residues at some level. What is said about the withdrawal periods for DES in feed is equally applicable to the required period between implantation of DES implants and slaughter of cattle with implants.

(1) *The Withdrawal Period.* A withdrawal period is the period before slaughter during which the animal feeder may not administer an animal drug. The withdrawal period allows the animal's body to dispose of some of the drug in its system. The approved withdrawal period for DES for both cattle and sheep feed is 7 days, 21 CFR 558.225. In 1974, FDA urged manufacturers to label their products for a 14-day withdrawal period (39 FR 11323; March 27, 1974). The agency has, however, taken the position that it will not approve supplemental NADA's to change the withdrawal date until the safety problems with respect to DES have been resolved; hence the continuation of the official 7-day withdrawal period in FDA regulations. Some manufacturers have apparently relabeled their drug for 14-day withdrawal (without objection from FDA), and others have not (Manufacturers' Exceptions at 46 n.*). Meanwhile, the Department of Agriculture has issued regulations requiring certification that DES was withdrawn from feed at least 14 days, before slaughter (9 CFR 309.16).

The manufacturing parties argue that, because 14-day periods are actually used, their NADA's should be evaluated on the basis of those periods. the statute is clear, however, that in deciding whether approval of an NADA should be withdrawn, the Commissioner is to consider whether new evidence shows that the drug is not shown to be safe for use "under the conditions of use upon the basis of which the application was approved," 21 U.S.C. 360b(e)(1)(B).

Should the manufacturing parties wish to seek approval of DES in feed under different conditions of use, they are free to do so. They must carry, however, the

burden of proving that the proposed new conditions of use are safe.

In order to provide as complete an analysis of the record as possible, however, I have made findings with respect to not only the 7-day withdrawal period but also the 14-day period. The latter findings assume, for purposes of argument, that the 14-day period is the approved withdrawal period.

(2) *Radiotracer Studies.* Several radiotracer studies were performed by scientists of the Department of Agriculture to determine the fate of DES in cattle and sheep. The results showed that very small amounts of DES remain in a number of different tissues of the animals treated with the drug.

In radiotracer studies, the scientist substitutes radioactive carbon (^{14}C) atoms for some of the non-radioactive carbon 12 atoms in the DES molecule. The molecule thus formed is biologically identical to the normal DES molecule except that it is now radioactive. The radioactivity allows the scientist to establish the absorption, distribution and excretory patterns of the compound of interest or its metabolites in biological systems, in this case, food-producing animals (G–76 at 3).

(a) *Oral Dosages in Cattle.*—(i) Studies. The currently approved conditions of use for DES in cattle feed permit up to 20 mg per head per day, with a withdrawal period of 7 days, 21 CFR 558.225. As discussed above, some manufacturers have labeled their products for a 14-day withdrawal period.

Two studies were done with cattle fed DES. The first, by Aschbacher and Thacker (G–2), involved the feeding to steers of a single oral dost of 10 mg ^{14}C-DES after the steers had been fed 20 mg per head of DES daily for 14 days. Because residues are observed in this type of study by detecting radiation in the tissues of treated animals (G–76 at 3), any radiation found would be attributable to the 10 mg of ^{14}C-DES. Cattle may be fed for up to 135 days (Tr. at 2023). Thus, total consumption of DES by a steer may amount to 2700 mg (20 mg × 135 days), or 270 times the amount of ^{14}C-DES administered in this study.

In this study, two animals each were sacrificed at 1, 2, 3, 5, 7, and 10 days after the ^{14}C-DES feeding. Dr. Aschbacher testified that radioactivity was observed in all sections of the gastrointestinal tract and in liver, kidney and bile-gall baldder in the animals sacrificed after 1, 2, 3, 5, and 7 days (G–1 at 3). The report of this test shows that some radioactivity was also observed in tissues of the steers sacrificed 10 days after the one-time ^{14}C-DES feeding (G–2).

The report of this study states the concentrations of radioactive material (above background) in the various tissues in the ppb equivalents of DES, on the assumption that all radioactive material is radioactive DES (G–2 at 1190, Table 4). The 7-day steers had, in their livers, 0.13 and 0.37 ppb. Standard deviations were listed as 0.04 and 0.07 for the first and second steers, respectively. After 10 days, 0.08 ppb (with a 0.04 standard deviation) was calculated for the livers of each of the two steers sacrificed. Therefore, the radioactive residues attributable to DES were found in livers of steers after more than the approved withdrawal period. The evidence from this study supports a finding that normal feeding of DES, even with a 7-day withdrawal period, results in DES residues in the animals' livers. This finding also applies by extrapolation to a 14-day withdrawal period. As discussed in the second paragraph of section III(B), tha amount of DES present after 7 days would decline but not disappear during the following 7 days.

It is true that the amounts of radioactivity found were small. The amounts of radioactive DES administered to the test animals also were small, however, compared to the amounts that are administered under the approved conditions of use.

The report notes that radioactivity was detected in the muscle of the steers sacrificed 24 hours, 5 days and 10 days after dosage, but not in the muscle tissues of other treated steers (id.). The manufacturing parties' Dr. Tennent stated his opinion that because of possible cross-contamination it is not possible to base any conclusions on the radioactivity found in muscle tissues (M–132 at 19). The Bureaus' Dr. Aschbacher also stated his opinion that no conclusions could be based upon the radioactivity found *in muscle tissues* of animals *sacrificed 5 and 10 days after dosing* (Tr. at 604). The published report of the study stated that ^{14}C-contamination did not appear to be an important factor in the liver, kidney, and bile-gall bladder samples when levels were above 0.1 ppb DES equivalents (G–2 at 1191).

In a 1975 report of his study to the Department of Agriculture, Dr. Aschbacher had also stated that, because of the low levels of radioactivity observed in muscle and the apparent randomness with which that radioactivity was seen there, he thought it was not possible to discount cross-contamination as the source of the radioactivity observed in muscle and carcass in the animals slaughtered after more than 24 hours (M–134 at 00097). With respect to the finding 24 hours after dosage, Dr. Aschbacher stated that the radioactivity observed in the muscle tissue was the result of the ^{14}C-DES dosage administered (id.). (He also noted that the fact that this residue was not analyzed meant that he could not conclude that DES was present. As discussed elsewhere, however, his analysis of other residues attributable to ^{14}C-DES showed that they contained DES and/or its conjugates, and I conclude therefore that this residue also contained DES or its conjugates.)

I do not rely upon the findings in muscle tissue in the animals sacrificed 5 and 10 days after dosage. I do, however, find that, as the researchers concluded (see M–134 at 00097), the radioactivity observed in the steers sacrificed 24 hours after dosage was a valid observation.

An isotope dilution procedure was used to characterize the radioactive material in liver tissues from two steers slaughtered after 2 days and one steer slaughtered after 7 days. Twenty-two percent of the radioactivity was confirmed as ^{14}C-DES in the 7-day steer and 36 and 46 percent were so confirmed, respectively, in the 2-day steers (G–2 at 1190–91). Thus, I find that at least a part of the residues found in liver in this study is either free DES or a conjugate that hydrolyzes to free DES. As a scientific matter, this finding is also applicable to the radioactivity detected in muscle 24 hours after dosage. Therefore, I find the feeding of DES to cattle in this study resulted in residues of DES or its conjugates in muscle as well as in liver. See discussion of the conjugates issue below (section III(C) of this Decision).

A second radiotracer study with cattle was performed by Dr. Rumsey, et al. (G–79). In this study, 7 heifers and 8 steers were administered 3 daily radioactive doses of 1.68 mg ^{14}C-DES after having been pretreated with 10 mg daily doses of unlabeled DES for at least 60 days. One heifer and one steer each were then slaughtered after respective withdrawal times of 0.75, 1.5, 3, 5, 7, 9, and 14 days. One steer was slaughtered 30 days after withdrawal. Radioactivity above the background rate (which indicates residues traceable to the ^{14}C-DES dosages) was found in all parts of the liver of the 7-day steer and in two of five parts examined from the 7-day heifer. Thus, this study provides evidence that doses of DES that, combined, represent a level one quarter the size (i.e., 5 mg v. 20 mg) of the daily dose approved for use, result in ^{14}C-DES residues in liver when the approved withdrawal period is

observed. Radioactivity calculated to be at or above the level of 0.2 ppb DES equivalents in wet tissues was found in the muscle tissues of steers sacrificed 0.75 and 1.5 days after dosing (see discussion of the significance of findings in muscle tissues in the conclusion of this section below).

Some of the liver tissues from the test animals were taken by the Bureaus to Dr. Kenneth Williams of the Worcester Foundation for Experimental Biology for further analysis. He subjected the samples to reverse isotope dilution procedures to determine the identity of the radioactive material in the livers. Dr. Williams reported that all of the samples tested, some of which were of livers of animals that had been slaughtered 7 days after dosage, contained DES and/or its conjugates (G–99 at 3). Dr. Williams, by further testing, confirmed that the DES he had discovered was not pseudo-DES (see discussion in section III(B)(2)(e) (G–99 at 5).

According to Dr. Rumsey, Dr. Williams' test showed the presence of 0.03 ppb of DES equivalents in the livers of the animals sacrificed 7 days after last feeding (G–76 at 4). Dr. Rumsey stated the results of the isotope dilution studies cautiously, saying that those results "suggested the possibility of but did not prove to me" the presence of DES in the livers (id. at 3). Dr. Williams, on the other hand, was unequivocal in his statement that DES and/or its conjugates had been found in the livers he tested (G–99 at 3). I accept Dr. Williams' evaluation of his own results in these tests.

(ii) *Conclusion As to Oral Dosage in Cattle.* The fact that radioactivity was found in some tissues of treated animals and not in others could be because (1) the study was not sufficiently sensitive to detect all DES residues in each tissue analyzed or (2) DES residues did not exist in the tissues in which radioactivity above background was not detected. Because DES was found in all tissues (including muscle) in the animals with the shortest withdrawal dates, and no viable theory has been proffered to explain why all DES would disappear totally from some but not other tissues, I accept the former explanation. I therefore find that these radiotracer studies establish that when DES is fed to cattle, it leaves residues of DES and/or its conjugates in the edible tissue (including liver and muscle) of treated cattle.

One ^{14}C-DES feeding test used a radioactive dose of 10 mg. The other used, in three doses, approximately 5 mg of radioactive DES. Resulting radioactive residues detected were small, but such residues were detected. It is fair to infer from these results, in the absence of evidence to the contrary, that had the ^{14}C-DES been fed at 20 mg daily for 135 days, the residues observed would have been larger. On the other hand, it is also fair to assume that a 14-day withdrawal period would have led to smaller residues. I find that, on balance, the studies' results show that DES feeding of cattle under approved conditions of use leaves residues in edible tissues (including liver and muscle), whether a 7 day or 14 day withdrawal period is observed.

(b) *Implants in Cattle.*—(i) *Studies.* The approved conditions of use for DES implants in cattle allow implantation of two 15 mg-pellets per animal or, alternatively, three 12 mg-pellets per animal "at the start of the feeding period or approximately 120 days before marketing," 21 CFR 522.640(d) (2) and (3). Two studies were done with steers implanted with DES pellets.

The first, performed by Dr. Aschbacher, et al., involved the implantation of four steers with 28 mg of radio-labeled DES. The steers were killed at intervals of 30, 60, 90, and 120 days after implantation (G–5 at 530). A control group was made up of four steers implanted with DES pellets not containing radioactivity. These steers were slaughtered on the 28th, 58th, 88th, and 118th days after implantation (id. at 531). The tissues from the control animals were used to establish a background rate for radioactivity.

Radioactivity above the background rate (and thus traceable to the ^{14}C-DES implant) was observed in all tissues from treated animals examined, including muscle, liver, kidney, adrenals, heart, etc., with the exception of the visceral fat of one of the 90-day animals (G–1 at 4; G–5 at 535, Table 2). The radioactivity in the livers was further characterized by isotopic dilution procedures and determined to be, in part, either free DES or a hydrolysable conjugate of DES (G–1 at 5; G–5 at 535). The report states that the amount characterized as ^{14}C-DES in the livers was equivalent to 0.07 to 0.13 ppb of DES (G–5 at 535). (These figures were apparently derived from a calculation based on the ^{14}C activity observed in the tissues and the specific activity of ^{14}C-DES.)

Part of one of the two ^{14}C-DES pellets in the animal slaughtered after 120 days had not dissolved and was retrievable at the time of slaughter (G–5 at 534; G–1 at 4). Thus, presumably, the implant was still delivering DES to the system at the time of slaughter.

A second study on cattle with implants was performed by Dr. Rumsey, et al., (G–77). This study involved the implantation of ^{14}C-DES pellets into eight steers. Two implanted steers and one control animal were slaughtered respectively at 30, 60, 90, and 120 days after implantation. All but one of the treated steers sacrificed received two implants totaling 32.2 mg ^{14}C-DES. One of the two steers slaughtered after 120 days, which was of a lighter weight, received only one implant of 15 mg (G–77 at 551, 554, Table 1).

The steers slaughtered after 120 days showed radioactivity significantly (p less than 0.05) above background in tongue, spleen, adrenals, lung, kidney, bile, and liver (G–76 at 5). One of the steers showed radioactivity significantly above background in cheek muscle (id.). Radioactivity above background was not found in shoulder or rib muscle or in the brisket (id.).

As in the feeding studies discussed above, the lack of a finding of radioactivity in some tissues in this study may be the result of either (1) the relative insensitivity of the tests or (2) the fact that no residues actually exist in these tissues. Acceptance of the former explanation is the conservative approach and is also supported by the findings in the Aschbacher implantation study. Therefore, I adopt it. Thus, although Dr. Rumsey's results may be taken as evidence that DES residues in the shoulder or rib muscle and brisket tissues are not found at as high levels as those found in other edible tissues (e.g., tongue, kidneys, livers), they do not show that no residues would, in fact, occur in shoulder or rib muscle and brisket.

In this study, like the Aschbacher implant study, part of the implant still remained in the steers 120 days after implantation (G–76 at 6; G–77 at 559).

Livers from this study were provided to Dr. Williams for characterization of the radioactivity observed. All of the livers were found to contain DES or its conjugates, including livers from animals slaughtered 120 days after implantation (G–99 at 3; cf. G–76 at 6). For the reasons stated in my discussion of Dr. Williams' analysis of livers from the feeding studies, his findings here with respect to livers apply also to other tissues.

(ii) *Conclusions As to Implant Studies in Cattle.* For the reasons discussed with respect to the feeding studies, I attribute the variations in the findings of radioactivity in the implant studies to inherent limitations in the levels of detection of the methods utilized.

As noted, approved conditions of use allow 30 to 36 mg implants inserted 120 days before slaughter. Since residues were observed (in the Aschbacher study

a residue was even found in muscle tissues), with implants smaller than the size permitted, 120 days after implantation (and also shorter periods after implantation), the results reported show that DES residues will appear at low levels in the edible tissues of cattle implanted in accordance with approved conditions of use. The fact that part of the DES implants still existed in some steers at the end of 120 days (and were thus presumably sending DES into those animals' systems at the day of slaughter) buttresses this conclusion.

(c) *Oral Dosages in Sheep.*—(i) *Study.* DES is permitted in sheep feed at up to 2 mg per head per day, again with a 7-day withdrawal period, 21 CFR 558.225. One study was done with sheep by Dr. Aschbacher (G–4). In this study, 6 sheep were sacrificed 7 days after feeding with a single dose of ^{14}C-DES. Neither the report nor the testimony is clear as to the amount of the ^{14}C-DES dose. Each of the sheep had been fed DES for the 7 days prior to the C-DES feeding, 2 at the rate of 100 mg per day, 2 at 4 mg per day, and 2 at 3 mg per day. DES feeding was continued in the first two groups for an additional 7 days but was stopped after the date upon which the ^{14}C-DES was fed in the third (3 mg) group. All sheep were sacrificed on day 15 (7 days following ^{14}C-DES dosing).

No measurable radioactivity was observed in the tissues of any of these sheep, with the exception of the adrenal glands in three sheep. In his testimony, Dr. Aschbacher stated that the design of this experiment and its analytical procedures would have prevented the quantitation of radioactivity present at the level of less than 1 ppb of DES equivalents in the animals receiving 4 or 3 mg of unlabeled DES per day (G–1 at 3). (He did not address the sensitivity of his methods as they apply to animals receiving 100 mg per day. The lack of sensitivity would also, however, mean that residues below 1 ppb from those animals would not be detected.)

(ii) *Conclusion As to Oral Dosages in Sheep.* The most likely reason for the failure of this study to show residues in tissues other than the adrenal glands is the relatively high limits of detection of the test methods. (Many of the residues observed in the cattle studies were observed at levels below the lowest level of sensitivity (1 ppb) of this test.)

The presence of DES residues in the adrenal glands of the sheep tested is evidence that DES residues remain within the sheep's bodies rather than passing totally out of their system. Because no rationale has been advanced to support a theory that all DES residues in the sheep's body would be concentrated in adrenal glands, I must conclude that DES residues would be present, at non-observable levels, in the other tissues of sheep fed DES.

My conclusion on this subject is supported by the results observed in the cattle studies discussed above. The fact that both cattle and sheep respond to DES by increased growth warrants, for present purposes, the assumption that the two animals deal with ingested DES in a similar manner. Such an assumption is biologically plausible (and more likely than the contrary assumption), and nothing in the record contradicts it. Both cattle and sheep are reminants and are good models for ruminant metabolism.

I find that the results of the radiotracer study in sheep, taken together with the evidence from the cattle studies, show that DES used under approved (or actual) conditions of use results in DES residues in edible tissues of treated sheep.

(d) *Implants in Sheep.* No radiotracer study was performed with implanted sheep. Although the question is not without difficulty, I conclude that the conservative approach appropriate for safety determinations sanctions extrapolation from the cattle data, despite species differences, to determine that DES implants in sheep result in DES residues in the edible tissues of sheep. I have discussed above my reasons for concluding that sheep are likely to deal with orally administered DES in a manner similar to cattle. The same considerations apply to DES implants. The results of the radioisotope test of DES fed to sheep (which showed that fed DES does remain in at least some tissue of these animals) also lend some support to the conclusion that DES implantation in sheep leads to tissues residues. I therefore find that the radiotracer studies show that use of DES implants in sheep in accordance with approved conditions of use results in DES residues in edible tissues of the treated animals.

(e) *The Pseudo-DES Issue.* The Court ordered a hearing on the withdrawal of approval of the DES NADA's in part due to applicants' argument that the residues identified by the radioisotope procedure were caused by an impurity in the DES implants supplied to the government researchers by Hess & Clark, *Hess & Clark, Division of Rhodia, Inc.*, v. *FDA*, *supra*, 495 F. 2d at 992. In particular, the applicants argued that the implants were contaminated with "pseudo-DES," which is somewhat similar in chemical structure to actual DES.

The Bureaus argue that Hess & Clark withheld the information that there were impurities in the implants until the radioisotope studies were completed and revealed that information only when it became in Hess & Clark's interest to do so (Bureaus' Brief at 62; see also the cross-examination of Dr. Tennent (Tr. at 1274–76)). The manufacturers, on the other hand, argue that they had forewarned the agency that there were impurities in the implants (Tr. at 1275). I need not decide this issue.

To resolve the pseudo-DES question, Dr. Williams further tested the liver samples from Dr. Rumsey's steer studies. These tests showed that the radioactivity identified by him as DES or its conjugates was, in fact, authentic DES or its conjugates and not the impurity, pseudo-DES (G–99 at 3–5; G–101; G–102).

Two of the manufacturers' witnesses discussed the pseudo-DES problem. One of them, Dr. Lieberman, admitted on cross-examination that in light of Dr. Williams' work all of the observed residue could not be pseudo-DES (Tr. at 2116).

The manufacturing parties' Dr. Tennent presented, in his direct testimony, calculations he had made from Dr. Williams' results. He stated that he had made corrections for contamination. He found 0.035 ppb of DES and its conjugates in the 120-day steer implanted with 1 implant and 0.120 ppb in the 120-day steer implanted with 2 implants (M–132 at 15). A table made up by Dr. Tennent for the samples taken from the orally dosed animals showed 0.037 ppb DES and conjugates in one animal slaughtered after a 7-day withdrawal period and 0.011 ppb in the other animal with the same withdrawal period (id. at 17). Thus, Dr. Tennent's analysis seems not to dispute the fact that there was some actual DES and/or its conjugates in the livers of some of these animals. Although Dr. Tennent stated that he considered the data marginal, due to inherent counting errors at low levels of activity (M–132 at 16), the record shows that Dr. Williams minimized counting errors by extending the counting time in his test procedure (Tr. at 684).

I find that the residues detected cannot be attributed wholly to pseudo-DES or other impurities. Whether or not, as the manufacturing parties' witnesses contend, some of the residues detected as DES and/or its conjugates are impurities, it is clear that part of the observed residues are in fact DES residues. I cannot find, for the reasons discussed below in the section of this Decision (sections III(C) and (D)) dealing with the carcinogenicity and other adverse effects of DES and its conjugates, that any amount of DES residues is safe. Therefore, the fact that DES residues have been shown to occur

at low levels in the edible tissues of DES treated animals (together with the evidence on toxicity discussed in section III(D) of this Decision below) is cause for concluding that the approved uses of DES have not been shown to be safe and have been shown not to be safe.

(f) *Conclusion As to Radiotracer Studies.* I recognize that application of the results of the radiotracer studies to approved (and actual) conditions of use involves, in some cases, extrapolation. Such extrapolation is commonplace in science and is valid here. For the reasons stated above, I find that the radioisotope evidence discussed above demonstrates that approved (and actual) animal drug uses of DES, in sheep as well as cattle, will result in DES residues in edible tissues.

(3) *Findings by Department of Agriculture Monitoring Program.*—(a) *Evidence of Residues.* The Bureaus rely upon evidence that DES residues have been discovered in animal tissue by the Department of Agriculture as part of its monitoring program.

Dr. John Spaulding, Chief of the Residue Evaluation and Planning Staff of the Department of Agriculture, testified concerning that Department's residue monitoring program. He stated that steer and heifer livers are selected at slaughterhouses by inspectors in accordance with (1) a random sampling technique (described in some detail by Dr. Levy (G–58)) and (2) a number of sampling procedures designed to follow up on evidence of potential violations with particular lots of meat (Tr. at 470–71).

A portion of the liver is shipped to a laboratory where it is analyzed by the gas chromatography method. This method can detect (but apparently not positively identify) DES at levels as low as 0.5 ppb (Tr. at 492–93). If the gas chromatography analysis is negative, the liver is considered to be free of DES residues (G–94 at 2). If the analysis is positive, the entire liver is then requested and a second analysis is performed, again using gas chromatography procedures (id.). If this test does not confirm the first result, the liver is not recorded as having been shown to contain DES residues (id.).

If the second gas chromatography analysis is positive, a third test is run (id.). If the level observed in the first two tests is high enough, this reconfirmation will be performed by mass spectrophotometric analysis (id.). This procedure can detect levels of approximately 2 ppb (id.). If the first two gas chromatography tests had detected DES at a level lower than 2 ppb, the gas chromatography procedure is performed yet a third time using a different derivative of DES (id. at 2–3).

A liver found to contain DES by one or both of the first two gas chromatography procedures but not by the third test (whether it be mass spectrometry or gas chromatography) is recorded as a presumptive violation (see G–58 at 2–3). Dr. Spaulding noted correctly that the conservative policy of the Department of Agriculture (USDA) in requiring confirmation of the first gas chromatography test by the second may result in an understatement of the number of residues that actually occur (G–94 at 3).

The Bureau submitted the testimony of Dr. Bert Levy, a statistician from the Department of Agriculture (G–58). Dr. Levy stated the number of cattle and sheep slaughtered during the years 1971 through 1975, the number of cattle and sheep tested for residues from 1971 through 1976, and the number found to contain violative levels of DES residues from 1971 through 1976. (The total number of cattle and sheep slaughtered in 1976 was not available at the time the testimony was submitted.) On the basis of these data he calculated, at a 95 percent confidence level, the percentage range (i.e., the lowest and highest possible percentage) of the total cattle and sheep slaughtered in that year that had violative DES residues. The numbers for cattle range from a low of 0.2–1.0 percent (reflecting 9 livers containing residues of an estimated 1780 tested) in 1976 to a high of 1.3–2.5 percent (reflecting 36 livers containing residues of 2003 tested) in 1972. Dr. Levy's calculations for sheep ranged from .09–0.6 percent in 1971 (5 livers containing residues of 1810 tested) to 0–3.7 in 1976 (0 livers containing residues of an estimated 100 livers tested).

Dr. Levy's calculations illustrate the fact that the number of DES residues found represents a much larger number of residues in the total treated population. If must be noted, however, that the percentages calculated depend more on the sample size than on the number of residues found. This fact is apparent from the calculations as to sheep stated above. In 1976, when 100 sheep livers were tested and no violations were found, the computed range of violations was 0–3.7 percent. This calculation is not intended to be evidence that the violation rate was as high as 3.7 percent. Indeed, as Dr. Levy's calculations show, the percentage of actual residues could be as low as zero.

The gas chromatography method of analysis was first supplemented by mass spectrometry in either 1974 or 1975 (compare Tr. at 496 (Dr. Spaulding) with Tr. at 725 (Dr. Levy)). Therefore, Dr. Levy's 1975 and 1976 figures (29 livers in 1975 equalling 0.8–2.7 percent violations and 9 livers in 1976 equalling 0.2–1.0 percent violations) were confirmed by mass spectrometry. The manufacturing parties emphasize that the gas chromatography method alone is not sufficient to identify residues positively as DES. This position is consistent with USDA's requirement of confirmation of gas chromatography findings by mass spectrometry in 1975 and 1976. In the table at the end of Dr. Levy's testimony (G–58), a number of apparent DES residues (15 in 1975 and 29 in 1976) are reported as presumptive violations, that is, violations that were found by at least one gas chromatography test but were not confirmed by "mass spectroscopy." (The term "mass spectroscopy" used in Dr. Levy's testimony is a synonym for the term "mass spectrometry" used elsewhere.) Because these residues have not been positively identified as DES, I place less weight on them than on the residues (stated above) that were confirmed by mass spectrometry.

As discussed above in the section on analytical methods, the gas chromatography/mass spectrometry method has not been shown to be sufficiently specific to serve as an analytical method for DES. Though this lack of specificity might make absolute confirmation of the residues as DES impossible, the USDA results are nevertheless probative evidence that DES residues exist in the tissues identified as containing DES residues by this method. An analytical method that does not meet all the requirements for routine regulatory use may nonetheless provide credible data for use in an evidentiary hearing.

The manufacturing parties argue that the Department of Agriculture findings of DES residues must be discounted due to three documents (M–18; M–19; G–28), which, they allege, show "apparent failures by Department of Agriculture employees to follow procedures that had been agreed upon with the FDA for the handling of samples of livers to be analyzed for residues of DES" (Manufacturing Parties' Exceptions at 49). The inference that the manufacturing parties seek to draw from these exhibits, i.e., that there was something wrong with the procedures utilized by USDA, is not warranted.

Two of the three memoranda reflect an agreement, reached in early 1974, to have USDA and FDA use the same method of gas chromatography analysis. An October 22, 1974, memorandum suggests that USDA had not made much progress in utilizing the agreed method (M–18 at 3). On April 18, 1975 (M–19),

the Bureau of Foods reported to the FDA's Associate Commissioner for Compliance that a new agreement had been worked out in accordance with which USDA would utilize the FDA method exclusively and then confirm by mass spectrometry the identity of any residues found. USDA would then report as positive any reading so confirmed. Neither of these memoranda shows that the procedures previously used by USDA were invalid, and thus neither provides a basis for disregarding the USDA residue findings.

The manufacturing parties take a sentence out of context from the third document referred to, a December 17, 1975, memorandum to the FDA's Chief Counsel from the Bureau of Foods (G–28), to imply that the FDA was not satisfied with the sampling technique utilized by USDA. In fact, the question raised there was whether USDA was cooperating correctly in a multi-laboratory test of the FDA's gas chromatography method. This document, also, provides no basis for disregarding the USDA residue findings.

It is apparent, therefore, that DES residues have been found in the past few years in the livers of cattle by the methods utilized by the Department of Agriculture's sampling program. (Although the majority of these residues appear to result from use of DES in feed, some result from the use of DES implants (Tr. at 769).) These residues have been identified in only a relatively small percentage of the animals tested, but it must be recalled that (1) not all residues will be caught by this system because the lowest level of measurement claimed is 0.5 ppb and (2) the residues found represent a significant amount of meat (1 percent of 25 million steers is 250,000).

(b) *The Question of Misuse.*—(i) *Necessity of Determining Whether Residues in Edible Tissues Result From Misuse.* The manufacturing parties argue: "The question * * * is whether the number of violations is so great as to show that the approved conditions of use are not 'reasonably certain to be followed in practice'" (Manufacturing Parties' Exceptions at 59). The question, however, is whether DES causes residues that have not been "shown to be safe," 21 U.S.C. 360b(e)(1)(B).

The manufacturing parties refer to 21 U.S.C. 360b(d)(2), which sets out factors that the Commissioner must consider in determining an animal drug's safety in the context of a *refusal to approve* an NADA. Because that section provides evidence of congressional intent with respect to the meaning of the term "safe," as used in the statute, it is appropriate to refer to it in a *withdrawal* proceeding as well. The section in question requires the Commissioner, in determining whether a drug is safe, to consider "among other relevant factors" four specified factors. One of these is "whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice," 21 U.S.C. 360b(d)(2)(D).

The manufacturing parties seem to argue that at some arbitrarily selected percentage of misuse of all animal drugs, "reasonable" misuse (to be tolerated) is divided from "unreasonable" misuse (to be the basis for a withdrawal). Then, they seem to argue, if residues are not found that prove that that percentage of misuse had been exceeded, the drug must be declared safe no matter how harmful the residues found may be to the consuming public.

This interpretation is inconsistent with the statute's terms. Whether conditions of use are reasonably certain to be followed is only one of several factors to be considered, and the ultimate issue is whether the animal drug is safe.

The term "reasonably certain to be followed in practice" must, in any case, be interpreted in the context in which it appears, i.e., as a consideration in deciding whether the use of a drug is safe. Thus, the amount of certainty that is reasonable necessarily varies with the danger posed by the drug. One degree of certainty would be required (i.e., reasonable) for a drug whose residue would kill a human consumer on the spot, whereas another degree of certainty would be required for a drug whose residue represented only a relatively remote danger to the ultimate human consumer. The failure to show the extent of the danger associated with residues of DES above 0.5 ppb (or above any level of residues—see section II(a) (2 and 3) of this Decision) prevents a determination that the reported residues are consistent with "reasonable" certainty that approved conditions of use will be followed in practice.

The manufacturing parties sought to introduce into evidence a document showing the extent of detected residues tolerated by the FDA for other animal drugs (M–148a). This document was properly excluded from the evidentiary record (see discussion of evidentiary rulings (section VI of this Decision) below). In any case, the argument that the percentage of residues detected for DES is no greater than the percentage of residues detected for other animal drugs is irrelevant. Because no safe dose for DES may be computed, DES cannot be compared to other animal drugs for which a safe dose can be computed.

Agency policy requires that the level of detection of the analytical method for an animal drug be set to pick up any residues above the safe dose for that drug. For carcinogens, a "virtually safe" dose or "no residue" level is utilized (G–24, see also 44 FR 17070; March 20, 1979). The percentage of detected residues for other animal drugs should, therefore, be the percentage above the safe dose. The percentage of residues computed for DES represents, at best, only the percentage of residues above 0.5 ppb, the lowest limit of detection of the gas chromatography method of analysis. We do not know how many residues occur above the "safe dose" of DES because no "safe dose" has been identified. Even if one accepts the Bureaus' witnesses' calculations of 1 ppt as a "virtually safe" dose, as I do not, no one knows how many residues occur above that level.

It is true that some animal drugs have been approved by the FDA using analytical methods that do not have a lowest limit of reliable measurement corresponding to a safe or "no residue" level by today's standards. Conceivably, some such NADA's may have been approved by mistake. Some are under review by the FDA now (see, e.g., 42 FR 43770; Aug. 30, 1977 (penicillin) and 42 FR 56254; Oct. 21, 1977 (chlorteracycline and oxytetracycline). (The cited documents are notices of opportunity for hearing in which one of the issues raised is whether the tolerance levels approved for those drugs are in fact, "safe levels.") The approval of other NADA's will be reviewed in an orderly manner in accordance with agency priorities pursuant to its ongoing "cyclical review" program (see 42 FR 64369; Dec. 23, 1977).

It may be that the FDA will find, after careful review, that it cannot determine the percentage of residues above a "safe level" or "no residue" level for these other animal drugs. If it makes that determination it will find, as I have done with respect to DES, that the existence of any amount of residues in edible tissues means that the approved conditions of use can not be found safe as "reasonably certain to be followed in practice." The comparison of the number of DES residues detected above 0.5 ppb with the number of residues detected for these other drugs is meaningless at this point.

I need not decide whether or not the residues found result from approved conditions of use. The residues present a safety question and (1) if they result from approved conditions of use, those conditions have not been shown to be safe or (2) if they result from misuse, then I can not find that the approved

conditions of use are reasonably certain to be followed, for the reasons discussed above. In either case, residues that have not been shown to be safe are entering the food supply in amounts that must be considered to pose a significant risk to the health of consumers.

(ii) *Evidence As to Causes of Residues.* I have, in any case, considered whether the record shows that the DES residues detected by USDA result either from following approved conditions of use or from misuse of the drug. The only evidence of potential value in resolving the issue are reports by FDA investigators. The Food and Drug Administration follows up on reports of DES residues made to it by USDA, in most cases by visiting the facility at which the animal was treated with DES. The Bureaus presented a set of approximately 140 establishment investigation reports ("EIR's") prepared by FDA inspectors who were seeking the cause of reported residues. This set of papers has been marked as Exhibit G–89. The Bureaus also presented a summary of EIR's from investigations of the causes of reported residues. That summary was marked as G–137.

The manufacturing parties note (Manufacturing Parties' Exceptions at 56) the discrepancy between the listing of the DES findings in Dr. Levy's testimony (G–58) and the DES residues noted in the summary of FDA investigations (G–137). For some years, G–137 lists more residues than does Levy; in other years, it lists fewer. The Bureaus have, however, explained this discrepancy: the FDA inspection figures are based upon not only the "objective" (i.e., random) sampling program described by Levy (see discussion above) but also the "for cause" program, which involves followup sampling of the products of previous offenders (Bureaus' Reply to Exceptions at 6). Thus, in those years when Levy reports more residues than the FDA, the FDA did not investigate each residue reported. Where the summary shows more residues, the FDA has investigated some residues found in the "for cause" program.

The manufacturing parties object to any reliance upon G–137 since the person who made up this summary was not presented for cross-examination. Some but not all of the EIR's summarized in G–137 were made part of the record as part of G–89. In reaching my decision I have relied exclusively on the EIR's actually made a part of the record in G–89.

The manufacturing parties suggest that only 12 of the 140 EIR's in G–89 do not show evidence of misuse (Manufacturing Parties' Brief, Appendix D at 1 n. *). Although my review of these EIR's reveals a somewhat larger number of EIR's lacking a showing of misuse, I cannot find that these reports demonstrate that DES residues occur when the approved conditions of use are followed.

Acceptance of the investigator's findings as evidence that residues will occur when the DES is used under approved conditions of use would reflect an unjustified confidence that where FDA inspectors had not found evidence of misuse there was no misuse. As misuse is a violation of the law, there would, of course, be incentive for feed lot operators to clean up before the FDA inspectors got to them. It would thus be surprising if FDA inspections caught the misuse in every instance. Therefore, I can not rely upon the relatively small percentage of investigations of residues that do not show misuse as proof that residues result when there is no misuse.

I conclude that the record does not permit resolution of the question whether the residues found by USDA are or are not the result of misuse of DES.

(c) *Conclusion As to Findings by USDA Monitoring Program.* The USDA reports demonstrate that residues in edible tissues do occur as the result of the use of DES pursuant to its approved (or actual) conditions of use, both in food and in implants, as an animal drug in cattle. The reports do not, due to the small number of tissues sampled in recent years, show whether or not use of DES as an animal drug results in DES residues in the edible tissues of sheep.

I conclude that it is not necessary to decide whether the residues found result from the approved conditions of use or from misuse of the drug. Whether or not the residues result from approved uses, the record demonstrates, as discussed in the sections on safety below, that these residues are potentially hazardous and have not been shown to be safe. To the extent that the possibility that DES will be misused is a factor in this safety decision, that factor does not support the safety of DES. The record provides no basis for a conclusion that the approved conditons of use are "reasonably" certain to be followed.

I have also made an alternative finding to obviate any need for remand in case a reviewing court should decide that I am obliged to determine whether or not observed residues result from misuse. That alternative finding is as follows:

(1) The observed residues result from misuse. Where the record does not contain sufficient evidence to decide a question, it is decided against the party with the burden of proof. As discussed above, the Bureaus have the burden of showing that residues are occurring under the approved conditions of use if a decision on that issue must be made at all. The Bureaus have failed in their burden, and the residues are therefore attributed to misuse.

(2) In light of the misuse demonstrated, I find that the approved conditions of use are not "reasonably" certain to be followed in practice.

(4) *GLC Residue Study.* Dr. Rumsey et al. performed one study of the fate of implanted DES in which radio-isotopes were not used (G–78).

Four lots of 16 steers were implanted with two 30 mg-DES implants each. Steers were sacrificed at 14 days, 28 days, 56 days, 84 days and 119 days. Animal tissues were analyzed, using identical gas chromatography techniques in two different laboratories. This test did not show the presence of DES in the tissues of animals slaughtered after more than 28 days. One of the two analytical laboratories found measurable DES in two of the animals slaughtered after 28 days but the other laboratory did not make that finding (G–76 at 2). The report of this study, and Dr. Rumsey, stated that the level of sensitivity of the gas chromatography method is 0.5 ppb (G–76 at 2; G–78 at 1). This study, as Dr. Rumsey stated (G–76 at 2), neither proves nor disproves that DES residues appear in tissues at levels below 0.5 ppb when DES implants are used in accordance with their approved conditions of use.

Part of the DES implants (about 20 percent of the initial weight) remained in the steers 119 days after implantation (G–76 at 2–3). This fact suggests that at least some DES implants remain in animals, releasing DES to their systems, 120 days after implantation. This finding supports my conclusion that approved conditions of use of DES implants result in residues in the tissues of the animals at slaughter.

(C) The DES Conjugates Issue

The Court in *Hess & Clark* stated as one issue to be considered in the DES hearing: "[W]hether the detected residues are composed solely of DES conjugates, and whether that substance is harmful; * * *", 495 F.2d at 994. The context indicates that the adverb "solely" refers to the manufacturers' arguments that the residues detected are solely DES conjugates as opposed to DES itself, and that the harmfulness of DES conjugates had not been put in issue.

Conjugates of DES are, according to the Bureaus' Dr. Kenneth Williams, "compounds composed of DES,

chemically linked to another molecule or molecules through one of its hydroxyl groups in such a fashion that hydrolytic [chemical or enzymatic] procedures may regenerate the parent compound" (G–99 at 2). Dr. Williams stated further: "In DES conjugates, the DES molecule is attached to another molecule but is otherwise structurally unaltered" (id.).

The manufacturers' Dr. Sieck stated under cross-examination that a test on which he was working had identified as conjugates of DES, the following: sulfate of DES, the monoglucuronide of DES, the monoglucuronide of methoxy DES and two other uncharacterized glucuronide conjugates (Tr. at 1370). Dr. Kaltenbach, another expert supporting the manufacturers' interests, stated that not all residues had been identified (Tr. at 2087).

(1) *Burden of Proof on Residue Issue.* The Court did not state who would have the burden of showing whether residues found are solely DES conjugates and whether those conjugates are harmful. It did make clear its rejection of the FDA's argument that a new discovery of unidentified residues is itself sufficient to show that an animal drug is no longer shown to be safe. The Court stated that the agency "has an initial burden of coming forward with *some* evidence of the relationship between the residue and safety to warrant shifting to the manufacturer the burden of showing safety. This is at least the case where, as here, the residues are of unknown composition" 495 F.2d at 993 (emphasis added); see also *Chemetron, supra,* 495 F.2d at 1000.

The question of what happens when new evidence shows that an approved animal drug adds unidentified residues to the human food supply is one of great importance to the FDA's ability to deal not only with DES, but also with other animal drugs. Chemicals such as animal drugs invariably are metabolized, at least in part, into other substances in an animal (or human) body. It is for this reason that the FDA requires identification of the principal metabolites of an animal drug, and demands toxicity testing and analytical methods for those metabolites, before it will approve an NADA (cf. G–24; 44 FR 17081 et seq. (March 20, 1979)). The agency's concern about these substances "formed in or on food because of the use of" the animal drug is in accord with the statute's requirements, 21 U.S.C. 360b(d)(2)(A).

Once an NADA is approved, as discussed previously, the agency can withdraw approval if "new evidence * * * shows that such drug is not shown to be safe," 21 U.S.C. 360b(e)(1)(B). Where new evidence shows that use of the drug results in residues of unidentified substances, the Commissioner must decide whether, despite his lack of knowledge of these substances, the drug may be considered to be "shown to be safe."

I reject the contention that the Court in *Hess & Clark* was demanding that the FDA identify the DES residues found and demonstrate that those residues are not safe. Such a requirement would place the public in danger during the period (perhaps years) necessary to characterize and test suspect residues of approved drugs. It would also put the FDA in the business of drug testing, a task that Congress intended to be the responsibility of the manufacturers of regulated products (see, e.g., H. R. Rept. No. 2284, 85th Cong., 2d Sess. 1 (1958)).

As noted, the Court in *Hess & Clark* did require "some evidence" of a link between the residue and safety before any burden is placed upon the applicant to identify observed residues and show their (and, thus, the approved drug's) safety. This requirement, not evident from the statute, is nevertheless met here. Those residues resulting from the use of DES that have been identified have been identified as DES and/or its conjugates (see, e.g., G–99 at 5–6; see also discussion above in section II (B) and discussion below). It is elementary biochemistry that the conjugation of a molecule, although it may change that molecule's activity quantitatively, rarely eliminates it.

This change in but failure to eliminate the activity of DES has been shown to occur with respect to the estrogenic activity of one conjugate of DES (see M–110 at 3; G–102: Comments on Vineland Laboratories Submission at 1; see also discussion in section III (c)(2) of this Decision below). Also, as discussed in detail below, DES conjugates would be expected to hydrolyze (break down) in the human body to form free DES, thus making DES conjugates as dangerous as DES itself. Therefore, there is substantial evidence in the record that warrants an inference that the DES conjugates are active in a manner similar to that of DES itself. Due to the recognized dangers associated with DES (see the discussion of the safety data with respect to DES below), there is, therefore, without question "some evidence" that residues identified as DES and/or its conjugates are unsafe.

Thus, if some evidence of a relationship between the residues found and safety is necessary, that evidence is present here. The manufacturing parties therefore have the burden of identifying the residues and showing them to be safe.

(2) *Failure of Manufacturing Parties to Satisfy Burden of Proof.* It is clear that the manufacturing parties have shown neither that the residues found are solely DES conjugates (rather than totally or partially DES itself), nor that DES conjugates are safe.

The manufacturing parties presented no data to show that all DES residues found would be in the conjugate form. They have not even advanced a theoretical basis that justifies an expectation that all residues would be conjugated.

The only investigation made of any of the residues detected to determine whether or not they contained free DES showed that in fact free DES residues were present, see G–103 at Tables V, VII, IX, X, XII, and handwritten tables. The Bureaus' expert witnesses did not rely upon this finding, however, and, as discussed below, the analyst who detected free DES noted that it can not be proven that the free DES he observed did not arise from hydrolysis of a DES conjugate during analysis (G–212: Comments on the Vineland Laboratories Submission at 1). I am thus left with a record devoid of support either for the proposition that the residues found are "solely" DES conjugates or for the converse of that proposition. The manufacturing parties have thus failed in their burden of proof on this issue.

Even assuming that all the residues discovered were DES conjugates, the manufacturing parties have failed to show that DES conjugates are safe. The only evidence in the record on this question is Dr. Kilman's testimony that DES-monoglucuronide had not caused renal (kidney) tumors in hamsters after 15 months (M–110 at 4 M–25) though it apparently did cause dysplastic changes in those animals (Tr. at 1827–28). (Cf. M–113 at 764 in which researchers suggest that it is a conjugated form of DES that is responsible for kidney tumors in hamsters.) The test cited by Dr. Kliman, of one animal species, for less than the animals' lifetime, in which the investigators looked only for one type of tumor, can hardly be accepted as evidence that DES conjugates are shown to be safe in man. It is perhaps noteworthy that the DES-monoglucuronide was administered subcutaneously in the hamster experiment (M–25 at 1252), a route that would be expected to prevent the metabolism of the glucuronide to DES itself (id. at 1255; M–110 at 3). As discussed below, the record provides evidence that DES conjugates are unsafe because they hydrolyze in the human body to DES itself.

Dr. Kliman also testified (M–110 at 3) that DES-monoglucuronide, when

administered by the subcutaneous route, had been shown in one test (M–111) to have 6 percent of the estrogenic potency (measured by effects on the cells of the vagina) of DES itself in rats and in another study to have 9 percent of the estrogenic potency (measured by effect on the weights of uteri) of DES in rats and 16 percent in mice (M–24). Dr. Kliman neglected to mention that the latter test showed that, when administered orally, DES-monoglucuronide had 40 percent of the estrogenic activity of DES in rats and 28 percent in mice (id. at 651). If one were to accept the manufacturing parties' argument that estrogenic activity is associated with carcinogenicity and toxicity, the evidence cited by Dr. Kliman in fact might be taken as some evidence that DES-monoglucuronide is unsafe. In any case, these data do not show the safety of DES conjugates.

Thus, I find (1) that the Bureaus have presented enough evidence (see subsection 1 of this section above) to raise substantial questions about the safety of the residues of DES; (2) that these residues consist of free DES or its conjugates or combinations of free DES and its conjugates; (3) that the manufacturing parties have not shown that the residues detected are solely DES conjugates; (4) that the manufacturing parties have not shown that DES conjugates are safe; and (5) that therefore the safety questions raised by the Bureaus remain unresolved. These findings, together with my finding (discussed above) that new evidence has shown that use of DES as an animal drug produces residues in edible tissues of treated animals, constitute a sufficient basis for withdrawal of approval of the DES NADA's.

(3) *Findings Assuming That Bureaus Have Burden of Proof.* The manufacturing parties read the Court in *Hess & Clark* and *Chemetron* as assigning to the Bureaus "the burden of coming forward with evidence sufficient to resolve * * * in their favor" the issues of the identity of the residues found and whether those residues are harmful (Manufacturing Parties' Exceptions at 70–71). I now consider the evidence in the record under this standard.

(a) *Evidence That Residues Contain Free DES.* Dr. Williams analyzed the livers of steers implanted by Dr. Rumsey et al. with radioactive DES (see, generally, G–99). (These radio-isotope studies are discussed in detail in section III(B)(2) of this decision.) Dr. Williams sought to determine whether any of the radioactive residues that were found in the livers of the treated steers were in fact free DES. He found free DES. (G–103 at Tables V, VII, IX, X, XII, and handwritten tables G–102: Comments on the Vineland Laboratories Submission at 1).

The manufacturing parties take the position that no free DES was actually found by Dr. Williams (Manufacturing Parties' Exceptions at 75–76). They focus on Dr. Williams' analyses of residues found in the liver samples from the two steers implanted with radioactive DES that were slaughtered after 120 days.

The attack on the findings in the first of these two liver samples is premised upon a mischaracterization of Dr. Williams' testimony on cross-examination. The manufacturing parties state, incorrectly, that Dr. Williams conceded that the amount of radioactivity detected in the "free fraction" of this first sample was so close to background radiation as to make his finding of free DES meaningless (id.). It is important to note, however, that Dr. Williams analyzed for free DES three separate subsamples of each sample of liver provided by Dr. Rumsey (see, e.g., G–103 at Table VII). At the hearing, Dr. Williams was asked about the subsample in which the radioactivity of the fraction of the residue identified as free DES was the lowest. He stated that the accorded no particular significance to the results for that subsample because they were so close to background (Tr. at 702). The manufacturing parties rely on this comment by Dr. Williams. The comment applies only to one of the three subsamples analyzed from the liver samples from the first 120-day steer. The fact that each of the three subsamples of the first liver sample produced a result above background provides more assurance that the result was a true one than would a single subsample standing alone. In addition, each of the other two subsamples of this first liver sample produced a result higher than the one about which Dr. Williams was questioned. Dr. Williams stated that he thought his findings for this whole sample (and the sample from the second 120-day steer) were significant (G–102: Comments on Vineland Laboratories Submission at 1).

The liver sample from the second 120-day steer produced slightly higher findings of free DES than the sample from the first steer. The manufacturing parties also attack Dr. Williams' findings with respect to the sample from the second 120-day steer, in part by taking out of context statements made by Dr. Williams.

"Counts per minute" are the units of measurement of the method by which Dr. Williams analyzed the residue. In the liver sample from the second 120-day steer, Dr. Williams observed free DES that provided a response of about 2 counts per minute above the background rate (Tr. at 702). The manufacturing parties rely upon statements by Dr. Williams dealing with his analysis of a different part of the residue (the hexane fraction) found in the livers (Manufacturing Parties' Exceptions at 76). He stated that "for these particular samples" (i.e., the samples tested in the haxane fraction analyses) 2 or 3 counts per minute would be "on a shaky line" (Tr. at 684) and elsewhere stated that 2.1 cpm would be "marginal above background" in the hexane analyses (Tr. at 691). While these statements were equivocal, I take them to mean that, *for the analysis of the hexane fraction*, 2–3 counts per minute was too low to produce a reliable result. Dr. Williams does not seem to have admitted, as the manufacturing parties suggest, that his findings in *his analysis for free DES* with the second 120-day steer were insignificant. In fact, he stated unequivocally that these results were not as was suggested to him during cross-examination, "meaningless" (Tr. at 702).

The manufacturing parties state that the Bureaus' Dr. Aschbacher testified that it was necessary to detect counts per minute of more than twice the background rate (not found for the two 120-day steers) in order to have meaningful results (Manufacturing Parties' Exceptions at 77). Yet the transcript reference cited makes it clear that Dr. Aschbacher's conclusion was applicable only to his own study, because of that study's design (Tr. at 597–98).

The manufacturing parties' witness Dr. Tennant stated his opinion that the low number of counts per minute observed in the residues found in the livers of the two 120-day steers were "marginal" (M–132 at 16). (Manufacturing parties' Drs. Lieberman and Kliman also made conclusory statements about the validity of the results observed with the 120-day steer livers (M–122 at 2, M–110 at 2).) The record shows, however, that Dr. Williams minimized the likelihood of error in his analysis by utilizing a relatively long counting time (Tr. at 684). I accept Dr. Williams' analysis of his own results.

The manufacturing parties argue that it has not been proven that an unidentified impurity was not responsible for the free DES observed Manufacturing Parties' Exceptions at 77–78). My conclusion that Dr. Williams'

results are not totally attributable to the impurity called pseudo-DES is discussed above in section III(B)(2)(c) of this Decision. There is no reason to believe that significant impurities other than pseudo-DES existed in the radio-labeled DES or that, if they existed, they would have caused the tests to reveal free DES erroneously. Thus, this speculation does not provide a basis for discounting Dr. Williams's observations.

The manufacturing parties do not attack Dr. Williams' finding of free DES at much higher levels in the ^{14}C-DES residues found in the tissues of steers slaughtered less than 120 days after implantation with DES (see G–103, Table VII.) They provide no explanation—and I am aware of none—for why free DES would be part of the ^{14}C-DES residues in animals slaughtered at less than 120 days but would not be part of residues found at 120 days (cf. Tr. at 2122). The results found with the sub-120-day samples thus confirm the results seen by Dr. Williams with the 120-day samples.

Although the results of Dr. Williams' analysis of livers from animals fed DES (as opposed to those implanted with DES) were not discussed, Dr. Williams' tables reveal that he also found free DES in the livers from the steers fed radio-labeled DES (G–103: handwritten tables). The manufacturing parties have suggested no reason why, in any case, the evidence on this subject from DES implants would not be applicable to DES used in feed.

I find therefore that Dr. Williams' analysis revealed free DES. This finding, however, does not necessarily mean that it has been demonstrated that use of DES as an animal drug results in residues that contain free DES.

According to the analyst, Dr. Williams, it can not "be proven that the free DES did not arise from hydrolysis of some conjugate (other than monoglucuronide) during the work-up of the samples" (G–102: Comments on the Vineland Laboratories Submission at 1). (Dr. Williams added tritium-labeled DES-monoglucuronide to some of the DES tested. His parenthetical exclusion apparently was meant to make clear that the free DES did not come from hydrolysis of the added product.) Dr. Williams' analysis thus shows that the residues contain either free DES or a conjugate hydrolyzable to free DES.

As I found in section III(B) of this Decision dealing with the detection of DES residues, the record shows that use of DES as an animal drug results in residues, in the edible tisues of treated animals, of DES and-or its conjugates. As discussed above, there is no reason to believe that these residues would be "solely" DES conjugates as opposed to DES itself. Based on the evidence in the record, however, I cannot exclude that possibility. I thus consider the question whether DES conjugates have been shown to be unsafe.

(b) *Evidence of Lack of Safety of DES Residues.* I find, on the basis of evidence in the record, that if the DES residues in the edible tissues of treated animals are conjugates of DES, those conjugates would be expected to break down (hydrolyze) in the human body to DES itself. Evidence in the record that DES is unsafe, therefore, is equally applicable to residues of DES conjugates.

The finding that the residues found, if they consist of DES conjugates to the exclusion of free DES, would nevertheless hydrolyze in the human body to free DES is supported by the testimony of expert witnesses. Bureaus' witness Dr. Williams stated: "I feel that it is most probable that conjugated DES, occurring in animal tissues, will give rise to free DES after ingestion by humans" (G–102: Comments on the Vineland Laboratories Submission at 2). Manufacturing parties' witness Dr. Liberman made clear his opinion that whatever DES conjugates were found in the radio-tracer studies would be hydrolyzable by enzymes to free DES (Tr. at 2123–24).

Evidence in the record that supports these opinions includes (1) studies (discussed in the following paragraphs) showing that one conjugate, DES-monoglucuronide, hydrolyzes to DES (apparently in the digestive tracts) in human and animal bodies (G–96–98) and (2) the discovery of free DES, discussed above, in the radioisotope tests of DES. (Evidence in the record shows that the free DES found by Dr. Williams either was an actual free DES residue or was the result of hydrolysis of a conjugate of DES. My reliance on the Williams's data here assumes the latter explanation to be correct. The William's study may be taken as showing that DES conjugates are hydrolyzed to free-DES. It does not, however, prove that the conditions necessary for that hydrolysis occur in the human body.)

Studies showing that a conjugated form of DES, DES–monoglucuronide, will be transformed back to DES itself in human consumers were introduced by the Bureaus' witness Ms. Weissinger (G–95). These studies were done with rats in various stages of early development (G–96–97) and, in one case, with two human volunteers (G–97).

In the human study, two men were each administered simultaneously DES-monoglucuronide labeled with radioactive carbon and DES labeled with radioactive tritium. Their excretory products were then analyzed. The researchers found that the DES-monoglucuronide and the DES itself resulted in simular metabolic products in the urine of the volunteers. (The different radioactive labeling of the DES and the conjugate made it possible to trace the metabolites to their parent compound.) This finding, together with other indirect evidence, showed that the conjugate was hydrolyzed to DES in the intestinal tract prior to absorption into the bloodstream (see, generally, G–97.)

Ms. Weissinger concluded that the rat and human studies showed that diethylstilbestrol glucuronide is hydrolized in the intestine to produce free DES (G–95 at 2). Ms. Weissinger stated her opinion that the conversion of the conjugate to DES in the intestine is catalyzed by an enzyme known as Beta-glucuronidase, which is present in microorganisms normally found in animal and human intestines (id.).

Manufacturing parties' witness Dr. Kliman attached Ms. Weissinger's conclusions on several grounds. Chief among them is that the upper part of the human small intestine does not contain bacterial glucuronidase, which Dr. Kliman stated is essential to the hydrolysis of the conjugate (M–110 at 18, cf. Tr. at 850 (Weissinger cross-examination)). Dr. Kliman stated that absorption takes place in the upper part of the human small intestine (M–110 at 18). Therefore, he seems to argue, hydrolysis of the conjugated DES would not take place at a point in the digestive tract at which absorption of the freed DES could follow. The test showed, however, that DES metabolites traceable to hydrolysis of DES-monoglucuronide did appear in the urine of the human volunteers (G–97 at 601, 602). They could not have done so had there been no absorption.

Dr. Kliman also argued that the studies referred to by Ms. Weissinger must be discounted because the subjects (both humans and rats) were fasting, and introduction of the DES with food might affect the absorption or hydrolysis being considered (M–110 at 17–18). In the absence of data showing that the results of such a study would have been different under nonfasting conditions, however, this criticism provides no basis for discounting the results.

Dr. Kliman further criticized Ms. Weissinger's testimony concerning the study on two human volunteers (M–110 at 18). Dr. Kliman argued that there is no evidence to show whether the conjugate of DES was absorbed in the presence or absence of its glucuronide component (id.). He then stated that there was no demonstration of conversion of the

conjugate to DES in the intestinal tract (id.). Neither of these points addresses the issue, however, because the study did show, according to its authors, that DES and the conjugate of DES administered simultaneously resulted in the same metabolic products in the body (G–97). The report of the study states further:

> Since the ingested glucuronide conjugate was excreted as products other than DESG [the DES conjugate], it appears that conjugate hydrolysis occurs in the body. Hydrolysis of DESG to DES may be nearly complete, since similar amounts of sulfate conjugates and polar non-hydrolyzable metabolites were excreted in the urine after ingestion of DES and its glucuronide conjugate * * *.

(G–97 at 601). Thus, there is no need to determine whether the glucuronide portion of the conjugate was present during absorption from the intestinal tract and subsequently removed or was split from the DES molecule before absorption. The material fact is that the conjugate was hydrolyzed to DES within the human system.

Steers have been shown to conjugate DES to DES-monoglucuronide (as shown by the presence, in the urine of steers treated with ^{14}C-DES, of DES-monoglucuronide attributable to that ^{14}C-DES) (G–3 at 47–48). This evidence supports a finding that DES conjugates found in edible tissues of cattle and sheep include DES-monoglucuronide.

In any case, as discussed above in subsection (a) of this section, however, analysis of residues actually observed in the radiotracer studies revealed that those residues contain, if not free DES itself, then DES conjugates that hydrolyze to DES. That evidence suggests the likelihood that whatever conjugates do occur in animal tissues will be hydrolyzed to DES in the human body.

(c) *Conclusion As to Conjugates Issues Assuming Bureaus Have Burden of Proof.* For the reasons stated, I find that, if the Bureaus have the burden of showing that the residues found are harmful, they have carried that burden. The residues contain either free DES or DES conjugates that would hydrolyze to DES. Because DES conjugates hydrolyze in the human body to free DES, the questions raised about the safety of DES apply equally to the conjugates of DES.

(D) Evidence That DES Is Not Shown To Be Safe

(1) *Relationship of DES to Endogenous Estrogens.*—(a) *The Issues.* As discussed below, DES is not a natural estrogen. Yet, because DES has estrogenic effects, the manufacturing parties contend that it should be judged as if it were in fact a natural estrogen (Manufacturing Parties' Exceptions at 94 ff).

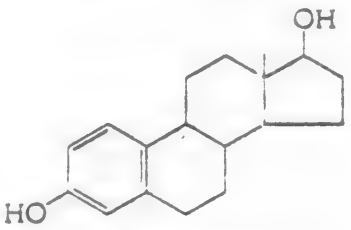
The manufacturing parties' theory is that the cancer and other adverse effects that natural estrogens cause occur only when those estrogens exceed the level at which they normally appear in the body (id. at 105–06). They argue further that the relatively small amount of DES added to the body through the ingestion (eating) of meat containing DES residues would not make the total level of estrogens in the body exceed normal levels (id. at 98–102), and that for that reason DES does not present a human cancer risk. It thus follows, they argue, that there is no danger in adding small amounts of DES to the human system (id. at 102 ff).

An assumption essential to the manufacturing parties' theory on this issue is that DES is simply another estrogen and that it has no carcinogenic or other adverse effects not associated with its estrogenic effects. The Bureaus dispute this assumption. They argue that there are significant differences between DES and natural estrogens and that DES may cause cancer and other adverse effects that would not result from natural estrogens at comparable dosages (Bureaus' Brief at 120 ff).

Manufacturing parties' witnesses seem to assume at the outset the proposition that they wish to support, i.e., that DES, which is not an endogenous estrogen, must be considered to be no different from an endogenous estrogen unless proven otherwise. They conclude, in effect, that because it has not been *shown* that all the adverse effects of DES are *not* associated with its estrogenic activity, it must be concluded that an association between DES estrogenicity and all of its adverse effects exists (see M–69 at 6 ("no compelling evidence" that tumor-enhancing properties not linked to estrogenic activity); M–110 at 6; M–62 at 5). Bureaus' witnesses, on the other hand, expressed the opinion that the lack of evidence that the adverse effects of DES *are* associated with its estrogenic activity prevents acceptance of that conclusion (see, e.g., G–80 at 8; Tr. at 164; G–90 at 6). Particularly in light of the demonstrated differences between DES and endogenous estrogens and the theoretically different ways in which the body deals with these substances (discussed below), I conclude that the record shows that DES cannot be considered as simply another estrogen.

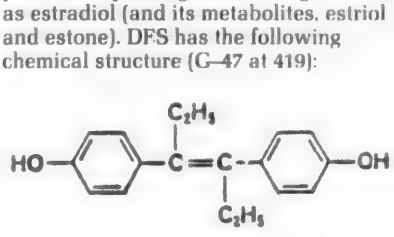
Even were DES "just another estrogen," it is by no means clear that it would be judged safe on that ground. The manufacturing parties agree (Manufacturing Parties' Exceptions at 97) that natural estrogens have been shown to cause cancer. See also Tr. at 1890; 2166–67. Estrogens have, in addition, been associated with other adverse effects (see, generally, 42 FR 37636, 37642 (July 22, 1977)). The fact that a dangerous substance occurs as a component of human tissues, cells, etc., (or is identical to a substance that so occurs) does not of itself justify approval of the addition of more of that substance to the human system by artificial means. *Cf.* I.D. at 35; *Bell* v. *Goddard, supra,* 366 F.2d at 182. Because DES can not legitimately be equated to endogenous estrogens, I do not reach the difficult question of how much (if any) of a substance chemically indistinguishable from endogenous estrogen could be added to the human body safely.

In discussing endogenous estrogens, the manufacturing parties refer most often to estradiol. Estradiol is a steroid (cf. G–189 at 2) that is produced by animals and man and is required for their proper functioning (cf. M–110 at 7). It influences biochemical physiological events associated with conception, birth, growth and development, and the proper functioning of adult individuals of the different species of mammals. The chemical structure of *beta*-estradiol (the most common form of estradiol) is as follows:

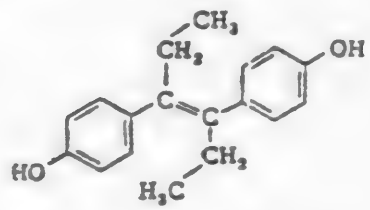


White et al., *Principles of Biochemistry* (5th Ed., 1973) at 1062.

DES is a stilbene (G–189 at 2; Tr. at 228). It is not produced by any species of animals, mammalian or otherwise, and is not required for the proper functioning of living organisms. It is produced synthetically. DES does, however, cause in mammals an array of physiological and toxicological effects that are remarkably similar to the effects produced by endogenous estrogens such as estradiol (and its metabolites, estriol and estone). DFS has the following chemical structure (G–47 at 419):



The manufacturing parties, while not disputing the validity of this rendition of the structure, proffer the following, which they apparently believe looks more like the structure of estrone given by the Administrative Law Judge (I.D. at 37 n. 23):



Manufacturing Parties Exemptions at 114, citing to Heftman & Mosettig, *Biochemistry of Steroids* (1960) at 167.

(b) *Differences Between DES and Natural Estrogens.* All parties agree that there are significant similarities between DES and endogenous estrogens. The hearing record establishes, however, that there are also incontrovertible differences in the chemical properties and in the biochemical and physiological effects of DES on the one hand, and estradiol (and other endogenous estrogens) on the other. For the reasons stated in the following discussion of these differences, I find, as did the Administrative Law Judge, that the observed differences bear on the toxicological significance of trace amounts of DES in meat from food animals.

(i) *Chemical and Biochemical Differences.* The Bureau's witnesses pointed to two areas in which the structural differences between DES and endogenous estrogens may lead to differences in effects. Each deals with the fate of DES and endogenous estrogens (specifically estradiol) within the body and raises unanswered questions about the claimed equivalence between DES and estradiol.

First, Bureaus' witnesses testified that there are differences in the way that the two substances bind to macromolecules in the body. These macromolecules, plasma proteins, attach themselves to smaller chemical molecules, such as those of estradiol and DES (G–191 at 2). Once bound, the molecules are hindered by the size of the macromolecule from leaving the circulation and reaching a target organ (id.) and, once there, entering the cell itself to do damage (Tr. at 73–74).

Although both estradiol and DES bind to the macromolecule albumin, estradiol, but not DES, binds to the much stronger binder, testosterone-estradiol-binding globulin (TeBG) (G–191 at 2). There is less TeBG than albumin in the body but TeBG binds so much more strongly to estradiol that its failure to bind DES must be considered significant. This is particularly the case because all active estrogens cause an increase in TeBG, i.e., the body protects itself from natural estrogens in a manner not available to counteract DES (id. at 3; G–90 at 6). Bureaus' witnesses point out that if significantly less DES than estradiol is prevented from reaching target cells, DES would be more dangerous than estradiol even if both had identical effects on the cell once they reached it (G–191 at 3; G–159 at 7).

It is noteworthy that this difference in binding resembles the effects observed in rats, though there it is alpha-fetoprotein rather than TeBG that causes the differential (G–159 at 2–7). Human alpha-fetoprotein binds well to neither estradiol nor DES (Tr. at 2309; M–203 at 5). Nevertheless, the analogy between rat experience with alpha-fetoprotein and human experience with TeBG, postulated by Dr. Sheehan (G–159 at 7), supports the question raised about differences in the human body's reactions to DES and estradiol.

The manufacturing parties' Dr. Jensen explained in proffered surrebuttal testimony his reasons for rejecting this theory. He stated that estradiol binding to TeBG is freely reversible, that albumin binds most estradiol, and that, even in pregnancy, TeBG binds only a relatively small fraction of the estradiol available (M–203 at 1–4). I explain in Part VI of this Decision dealing with evidentiary questions my reasons for agreeing with the Administrative Law Judge that Dr. Jensen's "surrebuttal" testimony was not proper surrebuttal and should not have been admitted. I have, nevertheless, considered his comments.

The record does not contain quantitative analysis of available data to support or reject either the theory that there are differences in the way DES and endogenous estrogens bind to macromolecules in the human body or Dr. Jensen's criticism of that theory. This potential difference between DES and estradiol, however, does raise an important question about the claim that the two substances are identical in their effects.

A second, less theoretical, area in which DES and estradiol are different is in the metabolites they produce. DES has been shown to yield, among other substances, dienestrol (3,4 bis (*p*-hydroxyphenyl)2, 4-hexadiene), *omega*-hydroxy dienestrol (3,4 bis (*p*-hydroxyphenyl)2-4-hexadiene-1-ol) (G–189 at 2–3; G–187 at 443) and *omega*-hydroxy DES (G–187 at 443; cf. G–189 at 3). Other substances, such as *para*-hydroxy-propiophenone, have been tentatively identified as metabolites (G–189 at 3). Bureaus' witness Dr. Helton testified that dienestrol and *omega*-hydroxy dienestrol are neither known nor expected to be metabolic products of any endogenous estrogen (G–189 at 3–4). No known metabolites of endogenous estrogens are similar to these substances in terms of structure or anticipated reactivity (cf. id.) This record does not provide a basis for determining whether the metabolic products unique to DES are the causes of some or all of the toxicity and carcinogenicity associated with DES (cf. M–203 at 5). I cannot discount the possibility that DES's metabolites exert effects that would not be associated with estrogens and their metabolites.

As the Administrative Law Judge noted, there is some evidence in the record that DES binds covalently to DNA (G–64 at 644) and is capable of damaging DNA (id. at 646). See also G–59 at 6. According to the manufacturing parties' own Dr. Jensen, such reactions are typical of chemical carcinogens foreign to the body or radiation, but are not typical of estrogenic hormones (M–69 at 6–7; see also Tr. at 2198; cf. G–59 at 6). Thus, the fact that DES and/or its metabolites is capable of binding with and damaging DNA is some evidence that DES may cause its carcinogenic effects (and other adverse effects such as teratogenicity and mutagenicity) by a mechanism that would not be expected of endogenous estrogens.

In their exceptions, the manufacturing parties attack the study that shows DES reactions with DNA. They argue that, of the two tests reported, one presented an artificial environment and the other produced only a relatively small effect (Manufacturing Parties' Exceptions at 122–23). The study that they contend involved an artificial environment does show that appropriately activated DES *can* react with DNA to modify it (G–64 at 644). The second study shows that this reaction does occur to some extent under more natural circumstances (id. at 646). These two studies do not provide unambiguous evidence that DES does indeed bind to and modify DNA. Yet the production by DES of reactions not expected to result from natural estrogens, like the production of metabolites not associated with natural estrogens, raises yet another unresolved question about the manufacturing

parties' assumption that DES is no different in its effects from endogenous estrogens.

(ii) *Physiological Differences.* The record establishes differences in the physiological (in this case, hormonal) effects of DES and those of estradiol. They are differences in the degree rather than the nature of the observed effects. For instance, the record shows the following: (1) Via the oral route, DES has about 10 times the estrogenic potency of estradiol (or of its metabolites estriol and estrone) (Tr. at 1784–5; cf. M–51 at 21, Table 3; cf. M–118 at 672 (20 times more effective in spayed mice)). (Estrogens cause cell proliferation and thus observable changes in the walls of the vagina. The potency of an estrogen is measured by, among other means, the extent of these changes.) (2) Intravenously administered estradiol is a more potent estrogen than DES administered via the same route in some species but not in others (M–110 at 9; see also M–115). (DES may be more potent relative to estradiol via the oral route than the intravenous route because by the oral route it is not oxidized (and thus neutralized) in the liver as estradiol is (cf. M–69 at 3).) (3) DES produces smaller changes in the vaginal mitotic index (changes in the rate of the multiplication of cells in the skin of the vagina) than does estradiol (M–40 at 4).

The differences in physiological effects between estradiol and DES shown by the record are of degree and not of nature. Endogenous estrogens may themselves differ in the strength of their physiological effects. Thus, the differences in physiological effects between DES and estradiol noted above would not be sufficient to reject the proposition that DES is no different from other estrogens.

Two points should be made about these data, however. First, the information in the record on the derivation of the comparisons noted above (see M–118) shows that they are based on effects observed at relatively high levels of DES and estradiol. These comparisons thus provide little usable information about the physiological effects, if any, of relatively small residues of DES in the edible products of animals treated with DES. Second, because of the differences in biochemical effects between estradiol and DES, I must reject the argument that these physiological effects of DES are necessarily related to its carcinogenic and other adverse effects.

I thus find that a comparison of the physiological effects of DES with those of estradiol (or other endogenous estrogens) neither supports nor detracts from the manufacturing parties' assumption that DES is equivalent to endogenous estrogens.

(c) *Conclusion As to Relationship of DES to Endogenous Estrogens.* In summary, the manufacturing parties have failed to demonstrate that DES is identical to estradiol (or any other endogenous estrogen) either in chemical structure or in biochemical or physiological (or toxicological) effects (cf. Tr. at 164–65; Tr. at 228–29). As Dr. Rosner stated, "There are differences [between DES and estradiol or other estrogens]. This is not the same compound" (Tr. at 2282; see also G–80 at 8; G–90 at 6). There are simply too many variables (and too many unknowns) inherent in the metabolic process and the processes leading to physiologic and toxicologic effects to conclude that DES is safe upon the basis of similarities to endogenous estrogens. In particular, the manufacturing parties have failed to establish that because the small amounts of DES introduced to the human body through residues in meat do not increase the body's level of estrogens DES presents no human cancer risk. On this record, I have no basis for concluding that the carcinogenicity of DES results entirely from its estrogenic activity.

(2) *Cancer Data.*—(a) *Animal Carcinogenicity Data.* DES is a carcinogen (G–22; G–34 at 1; G–37 at 2; G–46 at 2; G–47; G–59 at 2; G–70 at 2; G–80 at 7–8; G–84; G–85 at 6). This fact was stated unequivocally by one of the manufacturing parties' witnesses in a 1974 article that is part of this record (M–101 at 1920). This fact is also implicit in the analysis by the manufacturing parties of the results of the animal carcinogencity study conducted by Gass et al. (discussed below). (The manufacturing parties argue that, in that study, a carcinogenic response is observable in mice receiving 50 ppb DES and that that response increases with increasing dosage.) See also section I above.

Although the Bureaus submitted testimony to the effect that DES is a carcinogen in a variety of animals and NCI and IARC summaries of the studies showing that fact (G–47 and G–84), the only reports of animal carcinogenicity studies included in the record are the report of the Gass study and incomplete reports of an NCTR study.

(i) *The Gass Study. (a) Background.* The Gass study, entitled "Carcinogenic Dose-Response Curve to Oral Diethylstilbestrol" (G–22), appeared in the *Journal of the National Cancer Institute* in December of 1964. In this animal test, C3H female, C3H male and Strain A castrate male mice were divided into test groups that were given feed containing DES at the following levels: 0 ppb, 6.25 ppb, 12.5 ppb, 25 ppb, 50 ppb, 100 ppb, 500 ppb, and 1000 ppb. The test groups ranged from 50 to 78 mice. The three control groups ranged from 115 to 136 mice. The experiment was terminated after 85 weeks when the then surviving animals were destroyed in a fire.

A statistically significant incidence of mammary carcinoma was observed in the group of C3H female mice receiving the lowest dosage (6.25 ppb) of DES administered. The groups of C3H female mice receiving 12.5 ppb and 25 ppb did not show a statistically significant increase in tumors over controls. (Both of these treated groups showed tumors in 43.3 percent of the mice as opposed to 33 percent in the controls and 48.2 percent in the 6.25 ppb group.) There is no question that the C3H female mice fed 50, 500 and 1000 ppb DES developed mammary gland cancer and that the evidence of cancer in the treated groups increased with increasing levels of exposure.

The test groups of C3H male and Strain A castrate male mice were less sensitive. In each, some tumors developed in animals fed 12.5 ppb but statistical significance was not clearly apparent below the higher levels of exposure.

(b) Manufacturing Parties' Contentions. The manufacturing parties agree that this study (1) does not show that low levels of DES cause cancer and (2) does show that low levels of DES do *not* cause cancer, i.e., that there is a no-effect level (Manufacturing Parties' Exceptions at 126–27).

The first argument appears to assume that, if the only evidence that DES is carcinogenic was seen at dosages substantially above the levels of DES observed as residues, the FDA could not find that the levels observed as residues are unsafe or not shown to be safe. As discussed in the introduction to this Decision, however, the FDA must of necessity rely on tests showing effects of relatively high levels of a substance in test animals as a basis for the decision that lower levels of that substance present a carcinogenic risk to man. I have previously explained (in section III(D)(1) above) my reasons for rejecting the manufacturing parties' theory that the carcinogenicity of DES is related solely to its estrogenic activity. (If that theory were accepted, extrapolation from results of the ingestion of relatively high levels of DES in animals to predict the results of ingestion of lower levels of DES in humans might, of course, not be appropriate.)

In light of my rejection of the "carcinogenicity is a function of estrogenic activity" theory of the manufacturing parties, their second contention, that the animal studies show a no-effect level for DES, must also be rejected. Routine bioassays are not capable of establishing a no-effect level for a carcinogen. This proposition is well-supported by the opinions of noted cancer experts who testified at the hearing (G–46 at 8 (Dr. Hertz); Tr. at 172 (Dr. Saffiotti); Tr. at 1128 (Dr. Schneiderman); Tr. at 283 (Dr. Shimkin); *cf.* Tr. at 1176 (Dr. Herbst)). (The conflicting testimony of some manufacturing parties' witnesses is discussed below.) Thus, I can not find that the studies discussed in this section showed a no-effect level for DES's carcinogenic effect. This conclusion would stand even if the results of testing of DES at low levels were unambiguously negative. In fact, although the relative lack of sensitivity of the Gass study (G–22) makes interpretation of its results at low dose levels difficult, an apparent carcinogenic result was, as noted above, reported in that study at the lowest level tested (6.25 ppb).

Witnesses presented by the manufacturing parties supported those parties' contentions concerning the Gass study as follows: (1) Some witnesses gave their opinion that the lowest level of DES that cause a carcinogenic effect in the Gass study was a level (estimates varied as to what that level should be) above the lowest level of 6.25 ppb. (See, e.g., M–110 at 5; M–63.) (2) One witness testified that the results observed at the three lowest dosage levels of this study should be discarded because of the confounding effects of the fire that terminated the experiment (Tr. at 1948–51, 1969–70). (3) One witness testified that no valid statistical conclusions could be drawn from the study (M–139 at 8). My discussion of and evaluation of this testimony follows.

Neither the Bureaus nor the manufacturing parties called Dr. Gass as a witness. The manufacturing parties introduced an article authored by Gass and published in the Food, Drug and Cosmetic Law Journal (not a refereed scientific journal) in February of 1975. That article attacks the Delaney Clause. It comments upon Dr. Gass' own study as follows: "The lowest dose of DES that produces mammary cancer in the most susceptible animal species—the C3H mouse—required a minimum of 6.25 ppb—and probably four times that amount" (M–13 at 112). Elsewhere in the article Dr. Gass referred to the requirement of "at least" 6.25 ppb DES in a mouse diet to cause a carcinogenic effect and referred to the "probable carcinogenic dose level" of 25 ppb in the C3H mouse strain (id.).

Another manufacturing parties' exhibit (M–178) is a memorandum of conference between a Mr. Thomas Tomizawa and a Dr. R. L. Gillespie of the Bureau of Foods' Division of Toxicology. Dr. Gillespie, who apparently authored but did not sign the memorandum (dated March 23, 1976), quotes himself as having told Tomizawa "that currently Dr. Gass believed that 6.25 figure to be a biological fluke and that he believed the probability was that the true figure was somewhere between 25 and 50 ppb" (id.). The memorandum does not explain how Gillespie would know what Gass' then current beliefs were, and Dr. Gillespie was not called as a witness. Therefore the statement in the memorandum cannot be relied on.

No explanation is given by anyone as to why Dr. Gass was not called as a witness. Because the record reveals neither Dr. Gass' current views nor the basis for those views, and anyone disagreeing with them has not been given a chance to cross-examine him, I have accorded statements of his opinions less weight than those of witnesses who testified at the hearing. I cannot accept, without explanation, his apparent conclusion that some of the reported results of his study should be disregarded.

Manufacturing parties' witness Dr. Bernard Kliman explained his reasons for believing that the Gass study show that DES does not cause a carcinogenic effect at low levels (M–110 at 5):

> The log dose-response curve was linear only between 25 and 500 ppb. My further analysis of this data by extrapolation of this linear curve to intercept with the cancer incidence of the control animal group indicates no effect of DES on tumor incidence at or below 12.5 ppb.

Dr. Kliman disregarded the data points at the 6.25 and 12.5 ppb levels when fitting the probit-log dose line, and then noted that the observed responses at these two lower levels did not fall within the 95 percent confidence bounds of his extrapolated probit-log dose line (Tr. at 1832). It is not, of course, proper to exclude data from statistical analysis without evidence that those data are invalid.

Dr. Kliman, in dismissing the results at 6.25 ppb and 12.5 ppb, relied upon the fact that in the Gass study the lowest feeding concentration at which the weight of the ovaries was found to have decreased was 25 ppb. He stated: "It is reasonable to conclude that estrogens are associated with carcinogenesis only when given in amounts greater than the amounts required to produce a physiological response" (M–110 at 5). His only citation for this proposition was an article whose authors included Dr. Gass. This article contains basically that statement but provides no specific support for it. The article does state: "We should like to emphasize, however, that to the best of our knowledge, the relationship between the minimal physiological and minimal tumorigenic doses has not been determined for any of the estrogens" (M–64 at 23). (This article also contradicts the manufacturing parties' position on another point. In discussing the Gass study, it states: "As no levels below 6.25 ppb were fed, this study does not provide convincing evidence of a noncarcinogenic level in the C3H females," M–64 at 21.)

As discussed above, I have found that there is no basis for concluding that there is a direct relationship between the carcinogenicity of DES and its estrogenic effects. Thus, Dr. Kliman's exclusion of the results at 6.25 at 12.5 from his calculations makes his conclusions invalid.

The lead author of M–64, Dr. H. H. Cole, also testified for the manufacturing parties. Dr. Cole stated that physiological effects in the Gass study, i.e., ovarian weight depression, were noted at or about 13 ppb (M–62 at 3). (It is unclear where he got this figure.) He stated that 13 ppb would thus be the minimum level of DES required to cause a carcinogenic response (id.), although during cross-examination (Tr. at 1640) Dr. Cole admitted that at lower dosages there may have been physiological effects other than ovarian weight depression that went unnoticed. Dr. cole did not state a clear factual basis for his hypothesis of a link between observed physiological effects and carcinogenesis. I cannot, therefore, accept that hypothesis.

Dr. Cole cited a paper by Jones and Grendon (M–63) for the proposition that the Gass study showed that the minimum carcinogenic level for DES is greater than 27 ppb. A review of M–63 reveals no such conclusion. The authors of M–63 do state that Gass reported that "DES induces mammary cancer in mice only at levels causing physiological distrubances, not lower levels," (id. at 264). M–63 then refers to tables in the Gass study without commenting upon the finding of a statistically significant effect at 6.25 ppb in the female test animals.

Dr. Hardin B. Jones testified for the manufacturing parties (M–97). During cross-examination, he stated a new theory to explain the finding of a statistically significant carcinogenic

effect in the 6.25 ppb group in the Gass study (Tr. at 1948–51, 1969–70). Because this testimony was introduced only on cross-examination, the Bureaus were denied a chance to prepare detailed cross-examination of it. I have, however, considered Dr. Jones' theory on its merits.

Dr. Jones relies, in this theory, upon the fact that the Gass study was terminated when a laboratory fire destroyed the remaining test animals (G–22 at 973). The study called for sacrifice of any animal in which a palpable, one centimeter, subcutaneous mass was found. After sacrifice, the mass was examined histologically. Those masses diagnosed as "mammary carcinoma" were designated as tumors in the results (id. at 972). Those animals destroyed in the fire were, of course, not examined for tumors. The Gass results consider these latter animals as having no tumors.

Dr. Jones argues that one should exclude from analysis all animals lost in the fire. Having done that, he finds that the results in the 6.25, 12.25, and 25 ppb groups are not different at a statistically significant level from each other.

This lack of statistical significance, however, could be due to the reduction in group numbers and the consequent reduction in statistical power to detect differences. Moreover, the results of Dr. Jones' analysis are, in any case, dependent upon the number of animals per group that exhibit non-cancerous subcutaneous masses. If a group had a relatively small number of animals with such masses, then the percentage of animals with mammary carcinoma would increase, and vice versa. (The report of this study does not provide information about how many, if any, mice died of natural causes before the fire.) Because it is not clear that noncancerous subcutaneous masses were a controlled variable in these groups (and no adjustments can be made for this fact), it is not appropriate to utilize the method that Dr. Jones has suggested to analyze the results of this test. If it were, as Dr. Jones suggested, improper to count all of the animals destroyed in the fire as not having tumors, then I probably would be best advised to disregard this study altogether. The weight of the expert evidence, however, including testimony for both sides in this hearing, suggests that the test results can be relied upon when properly analyzed. (See, e.g., M–110; M–62; G–21; G–25.)

Dr. Thomas Jukes testified that the Gass study showed a dose-response relationship starting at 25 ppb and that this relationship" with an absence of significantly larger numbers of tumors above controls below this level" showed a threshold (M–99 at 4). this comment, of course, ignores the result observed in the 6.25 ppb group. Dr. Jukes then stated that any reliance upon the results observed in the 6.25 ppb group separately from the results observed in the groups fed 12.5 and 25 ppb DES "defies biological common sense" (id. at 5). The Bureaus do not, however, ignore the 12.5 ppb and 25 ppb results (see discussion below). Relyng on any of these three results "separately" would, of course, be improper.

Dr. Jukes also stated that the "threshold" for tumor induction of DES in C3H mice "extends at least as far as 12.5 ppb and perhaps to 25 ppb" (id. at 6). This conclusion is based upon his report that the NCTR study, discussed below, showed fewer tumors in mice fed 10 ppb than in control mice. I explain below my reasons for not relying on preliminary reports of the NCTR data. Another, and more persuasive, analysis of the combined low dose results from the Gass and NCTR studies would be, however, that these studies are not sufficiently sensitive to show clearly any effect that might be associated with very low dosages. This interpretation is the conservative one and I adopt it. Therefore, these data do not provide a basis for the conclusion that a threshold has been shown for DES.

The manufacturing parties suggest that, because C3H female mice are highly susceptible to mammary tumors (in part because of the presence of a mammary tumor virus in that strain of mice), the results of test with this kind of mouse are not properly applicable to man (Manufacturing Parties' Exceptions at 136–138). The particular sensitivity of these mice, however, only makes tests with them more sensitive indicators of the carcinogenic effect of a substance such as DES. I cannot find that this enhanced sensitivity is reason for discarding test results achieved in female C3H mice.

The manufacturing parties also contend that this animal test is not equivalent to human exposure because in the animal tests the feed containing DES constituted the entire diet of the mice and that mice consume more food per unit of body than humans do (Manufacturing Parties' Exceptions at 137–38). These factors only make this test more sensitive to carcinogenic reactions. For the reasons discussed in the introduction to this Decision (section I(D)), it is necessary to use the most sensitive animal test system available in seeking information about the potential carcinogenic effects of substances such as DES.

The manufacturing parties' statistical expert, Dr. C. R. Weaver, raised questions about whether the environmental effects and the diet effects were completely separated in the Gass study (M–139 at 8–10). It is true that, if there exists "confounding" of effects, it is nearly impossible to distinguish statistically between them. Dr. Weaver's concern is that in the Gass study all the cages of animals receiving a particular diet may have been together (but separated from the cages of animals receiving other diets), and that therefore the different diet groups were subject to different environmental conditions (M–139 at 9). Dr. Weaver relied upon secondhand hearsay for some of his assertions (Tr. at 1518). I have evaluated his statements in that light and do not consider his testimony a proper basis for a finding that the Gass study did not have a satisfactory experimental design to avoid the confounding of the effects observed.

Dr. Weaver stated that all interpretations of the Gass study should be disregarded until further evidence is available (M–139 at 8):

> In view of the inadequate nature of the Gass data, the anomalous results obtained, and the suspect nature of the data at the lower end of the dose range, it is my opinion that statistical conclusions cannot properly be drawn form this study. * * *

Dr. Weaver's position, if accepted, would mean that the Gass study could not be used to establish a no-effect level for DES. He thus directly contradicts the testimony previously discussed.

(c) Bureaus' Contentions. The Bureaus' contentions with respect to the Gass study are straightforward. They argue that the study shows (1) that DES causes cancer in test animals and (2) that 6.25 ppb DES caused cancer in mice in that study (Bureaus' Brief at 30, 41).

As discussed above, even some manufacturing parties' witnesses based their testimony on the conclusion that the higher levels of DES fed in this study produced cancer (see, e.g., M–110 at 5). That proposition is not fairly open to dispute, and I agree with the Bureaus that DES at least at the 50, 100, 500, and 1000 ppb levels was shown to cause cancer in animals in the Gass study.

Testimony in support of the Bureaus' second argument emphasizes that the 6.25 ppb result in logically consistent with the results observed at 12.5 and 25 ppb and, in turn, consistent with the hypothesis that any amount of DES would cause some carcinogenic effect.

Dr. Robert J. Condon testified that he had investigated whether or not the probit-log dose model for the incidence rate of mammary cancer among the

three sets of mice in the Gass study is appropriate (G–21). In order to make this determination, he carried out a Chi-squared test on each of the three data-sets (i.e., the results observed with each of the groups of mice tested). The Chi-squared statistic is based on the squared distances of the observed probit values from the fitted probit-log dose regression line. The calculated value is small if the observed probits do not deviate greatly from the fitted regression line; an absence of large deviation indicates with a high probability that the probit-log dose model is adequate.

Unlike the manufacturing parties' witnesses, who disregard the 6.25 and 12.5 ppb dosage levels in their computations, Dr. Condon used the data from all the dosage levels. He commented on his Chi-squared calculations as follows (G–21 at 2):

> The observed values do not differ significantly from those depicted by the fitted dose response curve at any of the doses used in this experiment. This means that none of the observed response values (mammary tumor incidence) should be dismissed as aberrant values.

If the probit-log dose model is accepted as correct, then there is no threshold level because this model presupposes that every dosage level induces a response.

Dr. Jerome Cornfield and Dr. Adrian Gross in effect incorporated in their testimony (G–25 at 2; G–34 at 1) a 1971 memorandum from Anne Alderman to Dr. R. L. Gillespie (G–23). (Ms. Alderman did not testify.) That memorandum also noted that the probit-log dose curve over the entire range of doses used could be observed in the C3H female mice in the Gass study. The interpretation of the Gass study data advanced by Drs. Condon, Cornfield and Gross is at least as persuasive as the manufacturing parties witnesses' conclusion (discussed above) that the results with the 6.25 ppb group are inconsistent with a dose.

The Alderman memorandum also contains the following observation (G–23):

> When the three lowest dosage groups (6.25, 12.5 and 25 ppb) are combined, they show a significantly ($P<.025$) higher incidence than the control group, indicating that there is evidence of an effect somewhere in this range.

Because the Gass study would not be expected to be sufficiently sensitive to produce interpretable results at levels in the 6.25 to 25 ppb range, I do not rely upon the argument by the Bureaus that this study shows DES to be a carcinogen at such low levels.

(*d*) *Conclusion As to Gass Study.* The testimony of the Bureaus' witnesses discussed above focused on the question whether the effect observed with the 6.25 ppb group in the Gass study was real. Preoccupation with the 6.25 ppb result threatens, however, to obscure the really important point about that study. No one, not even among the manufacturing parties' witnesses, disputed that this study showed that DES causes mammary cancer in mice in doses at 50 ppb and above. In fact, several manufacturing parties' witnesses agreed that there is a dose response relationship observable above that level.

If a substance causes cancer at the higher dosages in an animal assay and does not cause cancer at lower dosages, a scientifically sound interpretation of those results is that the test was not sensitive enough to detect the lower response that would be expected at lower dosages. Another conceivable interpretation of such results is, of course, that the dosages that did not cause an observed effect are not carcinogenic. Nothing in this record convinces me that the latter interpretation is the correct one and I cannot presume that it is.

I therefore do not rely upon a showing that 6.25 ppb DES did cause cancer in the Gass study. Rather, I rely upon the fact, discussed above in my evaluation of the manufacturing parties' contentions, that routine animal carcinogenicity tests currently cannot show a no-effect level for a carcinogen. (The support in the record for this proposition has been cited in my previous discussion of it.)

It is noteworthy that few carcinogens have been shown to cause cancer in animal studies at levels as low as 50 ppb, the level at which the Gass study unambiguously shows DES to cause cancer. Yet, the agency has not taken the position that no-effect levels have been established for carcinogens that do not show effects at levels that low.

The manufacturing parties, as noted, have argued that DES is different from other carcinogens because the carcinogenic effects of DES occur only at levels at which it causes physiological effects (such as ovarian weight depression (see M–62 at 3)) associated with its estrogenic activity. I have discussed in section III(D)(1) above my reasons for rejecting that theory. I must note that in any case the Gass study does not show, as the manufacturing parties contend, that there is a no-effect level for DES's estrogenic properties. An equally plausible interpretation of the data from that study is that the study was not sensitive enough to detect estrogenic effects below 25 ppb.

(ii) *NCTR Studies.* FDA's National Center for Toxicological Research (NCTR) has been performing relatively large scale carcinogenicity studies with DES. (Apparently manufacturing party Hess & Clark is also doing, or has completed, an animal DES study, whose results it has not revealed in the record (Tr. at 1460, 1469).) Neither the manufacturing parties nor the Bureaus were able to introduce evidence as to the final results of the NCTR studies. Each side, however, had witnesses testify about preliminary results that seemed to be favorable to its position.

The Bureaus introduced the testimony of Dr. Benjamin Highman of NCTR (G–54). Dr. Highman testified that he had examined tissue slide preparations of mice from one of the ongoing NCTR experiments (id. at 2). He stated that he found DES-related adenocarcinomas of the cervix and endometrium in test animals and did not find any such tumors in the control mice (id.). The number of such effects he had found as of the date of his testimony (March 22, 1977) was not large enough to be characterized as statistically significant (id.).

Dr. Highman's testimony was updated at the time of cross-examination (May 16, 1977) to include findings of additional tumors since the time when the direct examination was submitted (Tr. at 109–117). The additional information did not make the figures statistically significant (id. at 138). Dr. Highman noted, however, that the adenocarcinomas are extremely rare and he stated that the rarity itself made them significant from a pathological standpoint (G–54 at 2).

A manufacturing parties' witness, Dr. Jukes, testified that the NCTR had just completed (as of September 12, 1977) a a confirmatory experiment in which C3H mice received DES. He stated that the mice receiving 10 ppb of DES had a lower incidence of tumors than the control mice. From this information he drew the conclusion that the 6.25 ppb result in the Gass study represented insignificant fluctuation above the control value (M–99 at 5). This testimony was first stricken by the Administrative Law Judge and then reinstated (Tr. at 2141).

Dr. Jukes seems to have admitted at the time of cross-examination (November 4, 1977), that his statement that the test had been just completed was not entirely accurate, or at least did not mean that the histology and analysis had been completed (Tr. at 2140). During cross-examination, Dr. Jukes also agreed that his statement was referring only to mammary tumors and not to all tumors in the test animals (Tr. at 2206).

The question of how to deal with ongoing studies in an administrative

hearing is a difficult one. Until a test is completed and properly analyzed, reports of its results can be misleading. The FDA occasionally has to rely on preliminary analyses of test results in regulatory decisionmaking. It does so reluctantly and only in circumstances in which it has obtained all the information available about the study in question. The restrictions inherent in a regulatory hearing make full knowledge about the NCTR study impossible.

I have concluded that I should not rely upon the preliminary reports of results of the NCTR study. I have, however, considered whether my findings would change in any way if I were to accept as valid Dr. Jukes' report that the group of mice receiving 10 ppb DES in the NCTR study had a lower incidence of mammary tumors than control mice. For the reasons that follow, my findings would not change.

Dr. Jukes did not report that DES did not cause cancer in mice treated with higher levels of DES or even that those results did not show a dose-response relationship. As I have discussed, I must presume that the 10 ppb result, if reported correctly, is attributable to the insensitivity of the test system. That result alone, or together with the Gass data, would form no basis for determining that a no-effect level for DES's carcinogenicity had been identified.

(iii) *Conclusion As to Animal Carcinogenicity Data.* I find that DES is a carcinogen and that the results of the Gass study do not demonstrate a no-effect level for the carcinogenicity of DES. The NCTR data are not complete and cannot be relied upon. The results of the NCTR study reported by Dr. Jukes would not, at any rate, justify a finding that there is a no-effect level for DES. These findings warrant a conclusion that DES has not been shown to be safe and that it is unsafe.

(b) *Human Cancer Data.* It is entirely appropriate for a regulatory agency such as the Food and Drug Administration to conclude from data showing a substance to be carcinogenic in animals that that substance presents a caner risk to human beings. Indeed, FDA has done so often. See, e.g., *Certified Color Manufacturers Association* v. *Mathews*, 543 F.2d 284 (D.C. Cir. 1976) (Red No. 2); *Bell* v. *Goddard, supra* (DES as a poultry implant). The Bureaus have, in any case, presented expert opinion in this case to support the association between animal and human cancer. See, e.g., G–85 at 3 (Dr. Marvin Schneiderman). Thus, the evidence that DES is a carcinogen in humans is simply corroborative of the conceded animal carcinogenicity of DES, unless the human data can be said to show or to disprove the claim that very small amounts of DES have no effect when administered to humans. The data presented in the hearing do neither.

(i) *Dr. Herbst's Data.* Dr. Arthur L. Herbst discovered a link between the use of DES by expectant mothers as a drug to prevent miscarriage and a variety of changes in the genital tracts of female children born to those mothers. Chief in importance among these changes, which are manifested in most cases when the daughters are teenaged or older, is the finding of adenocarcinoma in the daughters' genital tracts. Dr. Herbst refers to these cancers as "clear cell adenocarcinoma," a type of tumor that he regards as rare (see, e.g., G–38).

After publication of his initial findings of a relationship between this type of cancer and maternal ingestion of DES, Dr. Herbst was instrumental in setting up and has directed a registry of clear cell adenocarcinoma in the genital tract of young females (G–37). Discoveries of this type of cancer have been reported to him and he has sought to determine whether each such cancer is, in fact, associated with maternal DES use. Dr. Herbst has reported his findings in a series of articles in medical journals (G–38 through G–43; G–45; M–26).

One hundred fifty-four of the 302 cases of clear cell adenocarcinoma reported in the most recent article were in women whose mothers had been treated with DES; 65 were not; 25 of the 302 reported cases were in women whose mothers had been treated with unidentified medication; and the history of the remaining 58 was uncertain (M–26 at 44). About 50 out of the 302 cases in his Registry were fatal. (G–37 at 3). (The Administrative Law Judge mistakenly states that 50 percent of the cases were fatal (I.D. at 25).)

Dr. Herbst referred to the "now generally-accepted relationship of these cancers to maternally ingested DES" (G–37 at 1). See also his statement that "the association of DES with these cancers is now an accepted fact" (id. at 2).

Dr. Herbst stated in his testimony that he was unable to calculate a risk figure to predict what percentage of those exposed to DES in utero will develop cancer (C–37 at 4). He stated that the "risk rate" through age 25 may be approximately 1 cancer per 1,000 exposures to the DES anti-abortion treatment, a risk that he regarded as significant (id. at 5). He declined to predict whether the rate will increase as the exposed individuals grow older (id.).

In a paper submitted by the manufacturing parties (M–26), Dr. Herbst and others utilized data obtained through his registry to make calculations of the risk of cancer from maternal DES use. These calculations are extremely questionable. They are based upon a ratio of the cases reported to him to the total number of female births during the various years in question. This ratio is then adjusted by a variety of estimates of the percentage of the total births in a given year that involved the administration of DES to the mother. It would appear obvious that the numerator (number of cases of this kind of cancer) would not represent all of the cases of this cancer during the years in question and that the denominator (number of births involving DES treatment of the mother) is based on speculation. The risk figure computed (for subjects 24 years old and younger) is between 0.14 and 1.4 per 1,000 (M–26 at 47). The only possible value of these calculations would be as an illustration that the number of DES-related vaginal tract cancers in proportion to the number of females exposed in utero is relatively small.

The Administrative Law Judge's decision summarizes the Herbst data, but does not discuss the manufacturing parties' attacks upon that evidence. Those attacks are four.

First, the manufacturing parties argue that Dr. Herbst has not shown a carcinogenic effect caused by DES. The manufacturing parties argue that the effect observed is teratogenic rather than carcinogenic (Manufacturing Parties' Exceptions at 142–144). Dr. Herbst himself has stated that the effect *may* be teratogenic (G–41 at 17 Tr. at 1165–66). This is also the conclusion of the manufacturing parties' witness, Dr. Jensen (see M–69 at 12). The teratogenic effect would be an alteration in the vaginal tract during the growth of the embryo that would lead occasionally to cancer (id.). The importance of this distinction is that a teratogenic effect leading to cancer would not be evidence that DES would cause cancer in those not exposed in utero. On this record, I have insufficient basis to determine that the effect observed cannot be characterized as carcinogenic. But in any case, a teratogenic effect would be a sufficient basis for a finding that DES is not shown to be safe.

Second, the manufacturing parties attempt to discredit the association between maternal use DES and the effects observed (Manufacturing Parties' Exceptions at 144–146). During cross-examination, Dr. Herbst was asked whether he knew what proportion of the mothers of affected daughters were diabetics or were taking insulin or were subject to high blood pressure. Dr.

Herbst answered that he did not know the specific figures, but that few were diabetic (Tr. at 1158–59). Dr. Herbst's responses to questions asked on cross-examination demonstrate that he did, in fact, look for other potential causitive factors for the cancers (id. at 1159, 1162). The manufacturing parties' attack on his data on that ground is thus not persuasive.

On cross-examination, Dr. Herbst stated that a high proportion of DES-treated mothers had a history of previous abortions or bleeding as a complication of pregnancy (Tr. at 1159). Since DES was used to prevent abortions, this fact would be expected (cf. Tr. at 1155, 1158). Manufacturing parties' witness Dr. Kliman appeared to suggest that the cases of vaginal adenocarcinoma found by Herbst might be associated with the saving of otherwise "high risk" pregnancies (M–110 at 21–22). Dr. Kliman criticized the failure of Dr. Herbst to compare his findings to a control group of comparable individuals (id. at 22). Dr. Kliman argued that the best control group would have been siblings of the treated mothers (apparently those siblings carried by the mothers during a time when they were not treated with DES (id. at 21–22)). Since, he apparently theorized, all these children would be dead (id.), by his definition such a comparison could not be made.

Dr. Kliman's argument is based upon speculation that there is some correlation between the need for DES as an anti-abortion agent and the cancer observed. He does not suggest a basis for this theory. Thus, while Dr. Kliman has pointed to another variable that cannot be controlled in the analysis of the Herbst data, his arguments do not form a basis for disregarding the association that Dr. Herbst has observed.

The manufacturing parties' third criticism of Dr. Herbst's data is that is shows effects only at "extremely high dosages" (Manufacturing Parties' Exceptions at 146–148). They argue that the Herbst data do not show a dose response relationship with DES and thus do not show that very small doses of DES cause a response. Dr. Herbst had identified one case in which the mother had received as little as 1.5 mg of DES per day or 135 mg during the entire pregnancy (G–39 at 716; G–37at 4), but the manufacturing parties argue that this result is consistent with the hypothesis that low amounts of DES do not cause the effects Herbst observed. They would lump this low dose case with cases reported for which there is no evidence that the mother was administered DES. Apparently the manufacturing parties are suggesting that all the other cases of DES-related cancers reported by Herbst involved very large doses of DES. Dr. Kliman testified that the usual dose for anti-abortion therapy was 5 to 150 mg per day (M–110 at 22).

The argument about size and dosage becomes important in light of the manufacturing parties' argument that any cancer-causing effect of DES is associated with its estrogenic properties. (See discussion of this question in section III(D)(1) above.) Thus, they argue that the dosage of DES administered as medication would be much greater than the amount of endogenous estradiol that humans normally produce (M–69 at 10). The amount of DES that might be consumed daily through ingestion of part per billion residues of DES in meat, on the other hand, would not add significantly to the amount of endogenous estradiol (id. at 10–11). As discussed in section III(D)(1), however, DES differs significantly from other estrogens.

The fourth manufacturing parties' attack on the Herbst data involves the charge that those data do not demonstrate a distinction between DES and natural estrogens (Manufacturing Parties' Exceptions at 148–149). Dr. Jensen argued that animal data show that abnormalities in developing reproductive organs, including production of tumors, can be induced with natural steroidal estrogens as well as with DES (M–69 at 14, 15). As discussed in section III(D)(1), however, DES is in some ways significantly different from natural estrogens. In view of these differences, I can not assume that natural estrogens, if used as DES was used in the treatment of pregnant women, would result in the abnormalities in their offspring observed as the result of usage of DES.

The attacks on the Herbst data, and on the conclusion that these data show an association between DES and cancers in humans, are thus without merit.

(ii) *Mayo Clinic Data.* In a study supported in part by FDA and NIH, 1,719 children born to mothers who had used DES during pregnancy at Mayo Clinic obstetric facilities from 1943 through 1959 were followed to determine whether any had developed cancers. No cancers of the vaginal or (for males) urinary tract were found. The authors of the report of this followup project concluded that their findings did not show a lack of correlation between DES and the vaginal tract cancer observed by Herbst. Rather, they concluded that their work showed the association to be rare (G–44 at 797).

The researchers calculated the upper limits of the risk from the use of DES as a carcinogen that would be consistent with their findings of no such cancer in 803 live born females. They calculated an upper risk limit with a 95 percent confidence level of 4 cancers per 1,000 exposed subjects (G–44 at 798). The researchers also considered the potential risk if their study were limited to those children of mothers exposed to DES during the first trimester of pregnancy. (The cases observed by Herbst had involved such exposure.) Using this group, and adjusting for the age of the patients at the time of followup, the researchers calculated an upper limit risk of 7 per 1,000 of developing this kind of cancer by age 13 and a risk of 13 per 1,000 of developing the cancer by age 22 (id.). It must be remembered that the results of this followup study are also consistent with a risk of zero per 1,000 for any of the groups considered. The upper risk limit is merely a function of the number of persons included in the followup group.

I accept the researchers' conclusion about this study—that it does not show that there is no association between maternal DES therapy and vaginal tract cancer in offspring but that it does show that that association is relatively rare.

(iii) *Chicago Study.* The University of Chicago sponsored a followup study of a controlled efficacy trial for DES use in pregnancy that had been conducted during 1951 and 1952. A report of early findings in this study was published in January 1977 and included in the record (G–10). A later, unpublished report of further progress of the study, submitted by the researchers to their contract monitor on August 31, 1977, was added to the record later (G–192). Each report states that no statistically significant correlations between cancer and DES treatment had been observed, either in the mothers treated or in the children exposed in utero. (There were other, noncancerous, effects of treatment. See section III(D)(3) of this Decision below.)

There were differences in the cancer incidences between the DES mothers and their control counterparts: 4.9 percent of the DES exposed women contracted breast cancer while 3.1 percent of the control women were similarly afflicted; 5.9 percent of the DES exposed women had cancer in "endocrine related sites" (breast, endometrium, ovary, and colon), while 4.2 percent of the control women had such cancers; 3.6 percent of the DES exposed women had cancers at other sites, while 2.7 percent of the control women had such cancers (G–192, Appendix 4–15a). None of these

increases was statistically significant, however.

The Bureaus, in their brief to the Administrative Law Judge, argued that G–192 illustrates that the increased risk of cancer in the DES exposed mothers was significant over time, i.e., that the DES mothers contracted cancer earlier than the control mothers (Bureaus' Brief at 34). Though the results reported do show that DES-treated mothers developed breast cancer earlier than women in the treated group (G–192, Appendix 4–14a), there is no showing that this effect is statistically significant.

The manufacturing parties submitted a statement of Dr. Herbst on this issue (M–209). In this proffered testimony, which was not received in evidence by the Administrative Law Judge, Dr. Herbst stated that he was now the principal investigator on the University of Chicago followup study, replacing Dr. Bibbo, who had authored G–192. Dr. Herbst stated that he, Dr. Bibbo, and the biostatistician involved in the research project agreed that G–192 did not establish that DES ingestion by mothers during pregnancy had caused an increased risk of breast cancer or that the report otherwise was evidence of carcinogenicity of DES in humans.

I concur with Dr. Herbst's analysis of this study. The data from the Chicago study taken alone would not be a basis for a finding that DES is a human carcinogen. Those data are, however, not inconsistent with that proposition. The results referred to by the Bureaus do raise questions about whether a larger, and thus more sensitive, study might show the effects the Bureaus contend exist.

(iv) *Conclusion as to Human Cancer Risk.* I find that evidence in the record concerning the incidence of clear cell adenocarcinoma in daughters of mothers treated with DES (the Herbst data) supports the conclusion (which may also be drawn from animal carcinogenicity data) that DES presents a human cancer risk. The evidence from the treatment of women with DES provides no basis for concluding that there is a no-effect level for DES with respect to cancer. These findings warrant the conclusions that DES has not been shown to be safe and that it is unsafe.

(3) *Adverse Effects of DES Other Than Cancer.* As noted above, the "safety clause" must be invoked if serious questions about the safety of observed residues are raised by the Bureaus, and the manufacturing parties fail to show that the DES residues are safe. I find that safety questions about DES have been raised not only by the substance's carcinogenic effects but also by other adverse effects with which it is associated. These questions have not been resolved.

(a) *Teratogenic Effects.* Dr. Thomas Collins of the Bureau of Foods testified about his review of articles suggesting a teratogenic effect associated with DES (G–12). He defined "teratology" as the science concerned with the generation of structural or functional alterations or malformations in organisms during their development, both prior to and subsequent to birth (id. at 1).

Based upon his review, Dr. Collins gave his opinion that DES is a teratogen in mice and humans and that it has specific effects on male and female reproductive systems and on the cardiovascular system (G–12 at 6; see also G–57 at 5; G–72 at 7–8). He based his conclusion on the following: (1) observations of anomalies of cervix development in females after prenatal exposure to DES (see discussion in this section below); (2) reproductive tract lesions in male mice exposed prenatally to DES in a study by McLachlan, et al. (see discussion in this section below); (3) observed effects on male genital tracts associated with the administration to the subjects' mothers of DES prior to the subjects' births (also discussed in this section below); (4) a letter to *Lancet* (the British Medical Journal) reporting one case of functional incompetence of male gonads, apparently associated with human prenatal DES exposure; (5) a report that four female human infants and children exposed to DES in utero exhibited a degree of masculinization, in a report that also stated that the offspring of 700 DES-treated women were shown to be normal; (6) three studies demonstrating teratogenicity of DES and DES dipropionate in mice; (7) a report that cardiovascular malformations were found at birth in children exposed prenatally to oral contraceptives during the first month of pregnancy at the rate of 18.2 per 1,000 versus 7.8 per 1,000 among children not so exposed. The reports relied upon by Dr. Collins are found in the administrative record at G–13 through G–20.

The manufacturing parties' Dr. Bernard Kliman contended that Dr. Collins' summary of published articles on the teratogenicity of DES is worthless "because he has failed to provide any analysis of these reports" (M–110 at 19). Dr. Kliman contended that these reports do not support Dr. Collins' statement that DES is a teratogen (id.). His own review of these reports was rather sketchy, and the criticisms he makes of them are not persuasive. Dr. Kliman discounted, for example, the three studies of Gabriel-Robez and colleagues (G–17, G–18, G–19) (the sixth basis for Dr. Collins' opinion as cited above) because DES dipropionate was administered instead of free DES (M–110 at 19)). DES dipropionate is, however, hydrolized by esterases (enzymes which catalyze the hydrolysis of esters into their alcohols and acids) to yield DES and propionate. Due to the abundance and ubiquity of these esterases, the proposition that DES was the underlying cause of the observed teratogenic effects cannot be disregarded.

One of the articles by Dr. Herbst details the benign abnormalities of the vaginal tract found in a study of 110 DES daughters and a control group of 82 unexposed females (G–40). He found an association with very high statistical significance ($p = < .0001$) between DES and the following abnormalities: vaginal or cervical fibrous ridges; cervical erosion identified in biopsy specimens; failure of part of the cervix to stain with iodine; vaginal adenosis identified in biopsy specimens; failure of part of the vagina to stain with iodine (id., Table 3).

These and other noncarcinogenic abnormalities observed in the daughters of DES-treated mothers may be characterized as "benign" (G–40 at 338). Any change in the human body caused by the administration of a foreign substance is, however, reason for concern. Although there is apparently no evidence of the direct transition from adenosis (the presence of glandular epithelium or its mucinous products), one of the observed abnormalities, to adenocarcinoma, it is noteworthy that adenosis is present in nearly all of the adenocarcinoma victims (id. at 339; see also G–42 at 10; cf. G–138 at 3).

Dr. Gill, in reporting his followup study of a controlled test of the effectiveness of DES in pregnant women (the Chicago study (G–10)), also observed statistically significant associations of maternal ingestion of DES with circumferential ridges of the vagina and cervix and dysplastic lesions in these tissues in female offspring. This study also demonstrated with statistical significance ($p < .01$ and $p < .005$) that DES is related to observations of epididymal cysts (the epididymis is the cordlike structure, near the testis, whose ducts store the spermatazoa), and hypotrophic (underdeveloped) testes in the male offspring. In addition, a substantial percentage (28) of the group of males exposed to DES in utero had severely pathologic decreases in sperm production; no such effect was found in the control males. Dr. Gill reported adenosis in 66.8 percent of the DES-exposed females compared to 3.6 percent in the control group. A later

report of this study (G–192), which includes more data, also found significance in these areas.

Dr. John McLachlan was an author of a book chapter (G–61) dealing with the transplacental toxicity of DES. It details a number of animal and human reports that have shown problems with the in utero exposure of animals and humans to DES. Some of the articles cited have been included in the administrative record. For example, G–60 is a report of a test of male mice exposed in utero to DES (100 mg per kg of maternal body weight administered daily from day 9 through day 16 of gestation). Six of 10 males born of DES-treated mothers were sterile, while none of a similar size group of males born to control mothers was sterile. Upon sacrifice, 15 of 24 of the males born to DES-treated mothers and none of the 15 males born to control mothers was found to have testicular changes (id. at 991).

Dr. McLachlan testified that carcinogens that require long term, high dose administration to induce detectable cancer in adult test animals have been shown to be capable of producing cancer in offspring of treated mothers at much lower doses administered for shorter periods of time (G–59 at 2). He identified this phenomenon as transplacental carcinogenicity and suggested that the human carcinogenicity data discussed above show DES to be a transplacental carcinogen (id.).

Dr. McLachlan is performing a series of studies on the teratogenic effects of DES (id. at 5). He described one such study, in which he observed a statistically significant dose response relationship between DES administration and loss of fertility of female progency of DES-treated mothers in a mouse study (id. at 4). The dosages range from 0.01 to 100 micrograms (μ) per kilogram (kg) of animal body weight. Although there was no statistically significant difference between the lowest dosage and the control animals, the dose-response relationship observed and the fact that higher levels caused an effect is significant.

Dr. Kliman objected to Dr. McLachlan's studies because "no control experiments were conducted with any natural estrogen (M–110 at 14), so that it is impossible to determine whether the observed effects would also have been caused by natural estrogens. However, Dr. McLachlan's objective was to ascertain the transplacental toxicity of DES, in which he succeeded, and not to establish that DES is the only estrogen that exhibits transplacental toxicity.

Dr. McLachlan described a theory that would differentiate DES from other estrogens with respect to transplacental toxicity:

> In the normal pregnant female, the presence of high levels of the endogenous estrogens may be less of a threat to the developing fetus because of the presence of *alpha*-fetoprotein, a substance that acts as a high affinity binder of natural estrogens and so renders them relatively nontoxic to the fetus. It has been demonstrated that DES does not bind to *alpha*-fetoprotein with the same high affinity (id. at 5).

In addition, he cited the same type of relationship in mammals for TeBG (discussed in section III(D)(1) above). For this and other reasons (id. at 6), it was his opinion that DES plays a more critical role than the endogenous estrogens in transplacental toxicity.

According to the manufacturing parties' Dr. Bernard Kliman, Dr. McLachlan misinterpreted the data of Uriel, et al. (G–63) in developing his theory. Dr. Kliman stated that DES has 40 percent of the activity of estradiol and nearly the same activity as estradiol in binding to these proteins. Also, the lower binding activity of DES only allows DES to be metabolized more quickly by the liver (M–110 at 15–16).

As discussed in section III(D)(1) of this Decision, data sufficient to resolve the arguments presented by Dr. McLachlan and those presented by Dr. Kliman on this issue is lacking. It is therefore not possible to determine with assurance that the teratogenic (or mutagenic) effects of DES either differ from or are the same as the effects associated with endogenous estrogens.

I must conclude, on the basis of the evidence discussed in this section, that DES is a teratogen in animals and in humans.

(b) *Mutagenic Effects.* Dr. Sydney Green, who, at the time of his testimony, headed the Genetics Toxicology Branch of the Division of Toxicology, Bureau of Foods, reviewed two published reports (G–32 and G–33) that establish the mutagenicity of DES diphosphate. The first study revealed that DES diphosphate resulted in monosomies (cells with one chromosome less than normal) and trisomies (cells with one chromosome more than normal) in the bone marrow of mice (G–32). Dr. Green classified this as a mutagenic effect (G–31 at 2):

> The monosomies are not significant contributors to hereditary diseases or disorders because cells possessing such chromosomal abnormalities rarely survive. However, the presence of trisomies can be said to be a true mutagenic effect. Such cells usually survive and pass on their abnormal characterisitcs to future generations. If these effects are seen in germinal (sex) cells they can lead to mongolism and other hereditary disorders.

The second study also uncovered the production of trisomies in offspring of mice whose mothers were treated with DES diphosphate (G–33).

During cross-examination, Dr. Green stated his opinion that DES could be considered as the underlying cause of this mutagenic effect (Tr. at 578–79). He noted, among the bases for his opinion on this issue, the fact that when DES diphosphate is hydrolized it yields DES: "So, in essence, one would be testing diethylstilbestrol within the cells, as opposed to diethylstilbestrol diphosphate"(Tr. at 579).

Dr Kliman criticized the testimony of Dr. Green, particularly because Dr. Green failed to mention that similar mutational aberrations are also associated with the natural estrogens (M–110 at 20). But, during cross-examination, Dr. Green acknowledged that studies have shown estrogens to be mutagenic (Tr. at 578–79). Like Dr. McLachlan, he did not claim DES is the only estrogen that produces adverse effects.

I find, on the basis of the evidence in this record, that DES does cause mutagenic effects in some circumstances.

(c) *Other Effects.* Dr. Roy Hertz reported on the extreme potency of DES evidenced by accidental absorption in industry and the home, such as "the occurrence of breast development in children ingesting accidentally DES contaminated vitamin capsules," and "the precocious development of the breasts and external genitalia when the prepubertal daughter of a worker (in the animal drug industry) used her father's bed while he was at work" (G–46 at 7). These reports add marginally to the impression that DES poses genuine and serious risks to humans and that its activity produces toxic effects that are not now totally understood.

(d) *No-Effect Level.* The Bureaus' witnesses testified that no-effect levels for the adverse effects of DES could not be established. With regard to the teratogenic effects of DES, Dr. Collins testified that "none [of the reports he evaluated] are sufficiently complete to allow us to establish safe tolerance levels for DES" (G–12 at 6). Dr. Gill, who reported on the effects of DES discovered in the Chicago study, stated that "it is not possible to calculate a safe tolerance level for such exposure for the data reported" (G–138 at 3; see also G–37 at 5).

Dr. Kilman testified that Dr. McLachlan's work points to a no-effect level of DES because "female mouse

fertility was not significantly altered by the lowest dose, 0.01 μg per kg per day on days 9 to 16 of pregnancy" (M–110 at 14–15). The failure of this test to demonstrate a response at its lowest dosage could, however, be the result of the relative lack of sensitivity of the test system. Dr. McLachlan himself testified that it is not possible to determine a no-effect level from his studies (Tr. at 92).

Dr. Green testified that the mutagenic studies he reviewed also did not support the existence of a no-effect level for DES:

> These studies, however, do not provide quantitative data which would allow a calculation of a no-effect level for these effects and the subsequent estimation of safe tolerance levels for humans (G–31 at 3).

(e) *Conclusion As to Adverse Effects of DES Other Than Cancer.* I find that the evidence presented by the Bureaus demonstrates that DES is a teratogen and a mutagen. It is not possible from the evidence in this record to establish the existence of a no-effect level for DES for these effect. Thus, the fact that DES causes teratogenic and mutagenic effects is an independent basis for my conclusion that DES has been shown not to be "shown to be safe," and that it is unsafe, for its approved uses.

(E) *The Risk-Benefit Issue* (1) *Propriety of Risk-Benefit Analysis.* The Administrative Law Judge held that under 21 U.S.C. 360b consideration of the alleged societal benefits of the use of DES is not an appropriate part of the decision whether approval of the new animal drug application should be withdrawn (I.D. at 15). This interpretation of the statute is supported by the legislative history of the statute, is consistent with positions the agency has taken previously on this issue, and reflects sound public policy. In *Hess & Clark, Division of Rhodia, Inc.* v. *FDA*, 495 F.2d 975 (D.C. Cir. 1974), however, the Court stated in *dictum* that the FDA should consider the benefits of the use of DES should it proceed under the "safety clause" (495 F.2d at 993–94):

> Outside of the per se rule of the Delaney Clause, the typical issue for the FDA is not the absolute safety of a drug. Most drugs are unsafe in some degree. Rather, the issue for the FDA is whether to allow sale of the drug, usually under specific restrictions. Resolution of this issue inevitably means calculating whether the benefits which the drug produces outweigh the costs of its restricted use. In the present case, DES is asserted to be of substantial benefit in enhancing meat production, and this is not gainsaid by FDA. The FDA must consider, after hearing, whether DES pellets would be safe in terms of the amounts of residue consumed. (Footnotes omitted.)

Early in 1977, the manufacturing parties filed a motion in the United States Court of Appeals for the District of Columbia Circuit to compel the agency to consider the societal benefits from DES, including any adverse environmental consequences from withdrawal of the NADA's, as part of the hearing. In a memorandum of March 22, 1977, Acting Commissioner Gardner mooted that question by directing the Administrative Law Judge to consider the benefits issues. He did so by means of a memorandum to the Administrative Law Judge in which he noted that he was taking no position on the relevance of these issues to the proceeding. He did state in that memorandum: "In making this safety determination [under the "safety clause"] societal benefits and environmental effects have historically not been considered to be legally relevant" (Record No. 110 at 2).

(a) *Legislative History.*— (i) *New Animal Drug Provisions.* The new animal drug applications that are the subject of this hearing are creatures of the animal drug amendment of 1968. As noted in section I, that amendment was intended to consolidate the agency's review of animal drugs, which was at that time being conducted under the food additive amendments and the new drug provisions. Congress did not, in writing the new animal drug provisions, include language authorizing the FDA to consider the benefits of an animal drug in determining whether it is safe. (Compare 21 U.S.C. 346 and 346a, in which Congress required the Commissioner and (now) the Administrator of the Environmental Protection Agency to consider the benefits of the products regulated under those sections in the setting of tolerances.) Nothing in the legislative history of the 1968 amendments supports the proposition that the FDA should consider the socio-economic benefits of a drug in deciding whether it is safe. The manufacturing parties have, however, relied upon legislative history of the new drug and food additive provisions for support of their position that benefits should be considered. Little support exists.

(ii) *New Drug Provisions.* DES was approved for animal use in the 1950's under the then-existing new drug provision. Prior to 1962, when effectiveness was made an additional consideration, new drug applications were approved if use of the drug was shown to be safe. At that time, the agency took the position that effectiveness was an element in the consideration of the safety of a drug when that drug was to be used in treatment of a life-threatening disease or where there was an indication that that drug would occasionally produce serious toxic or even lethal effects. The manufacturing parties argue that, in taking this position, the FDA was stating its understanding that a safety determination necessarily involved a risk-benefit analysis.

The evident flaw in the application of the manufacturing parties' argument to the instant proceedings is that effectiveness in a human drug context is different from effectiveness in an animal drug context. The risk to the patient from a human drug may be justified by a therapeutic benefit *to that patient* from the drug. It is an entirely different question, however, whether the risk to human consumers of the products of animals are justified by an economic benefit to animal drug manufacturers, animal producers, or meat consumers generally.

(The only time where the theory that effectiveness is part of safety would be applicable to an animal drug would be circumstances in which the risk was to the animal itself, as opposed to any human consumer. FDA considers that type of benefit relevant to a determination of safety; but that type of benefit is not at issue in this proceeding. The types of benefits urged by the manufacturing parties are alleged health benefits to humans and economic and environmental benefits.)

There is, of course, an obvious difference between the therapeutic benefits of a drug, which often alleviate a risk to the person to whom the drug is administered, and so-called "socio-economic" benefits associated with the use of a drug. The former are the *only* type of benefits that the FDA considers in determining whether a human drug is safe. The agency never considers socio-economic beneftis in making that decision.

Moreover, the consideration of risks and benefits with respect to human drugs is always based on the premise that before being exposed to the risk, an individual patient will have the protection of either a physician's evaluation (in the case of a prescription drug) or adequate directions for use enabling the patient himself to decide whether to run the risk (in the case of an over-the-counter drug). No such protection is available to those exposed to the risk from residues of DES in meat.

The asserted similarity between the treatment of human drugs and animal drugs is, of course, critical to the manufacturing parties' argument on this subject. Apparently the distinction between the two systems of regulation was not adequately pointed out to the

Hess & Clark Court, however. In a footnote, the Court quoted extensively from an article by Richard Merrill on prescription drug injuries as support for the proposition that effectivenss considerations are relevant to safety determinations (495 F. 2d at 994 n. 59).

(iii) *Food Additive Provisions.* The manufacturing parties rely upon the fact that one impetus for passage of the food additives amendment was a desire by the FDA and the regulated industry to allow FDA to set tolerances for products that were hazardous at some levels and not at others. Congress, in accommodating this desire by allowing the setting of tolerances, allowed the agency to consider the level of the ingredient that would be required to serve its functional purpose. Where a tolerance limitation is required for a product, the tolerance may not be greater than the amount necessary to accomplish the additive's intended purpose; see 21 U.S.C. 348(c)(4)(A). Similarly, where a tolerance is required, no food additive petition may be approved unless it contains evidence that establishes that the additive will accomplish its intended physical or other technical effect; see 21 U.S.C. 348(c)(4)(B).

Thus, where an additive is shown to be safe at some level, the FDA is authorized to consider whether it does what it is intended to do. The FDA is not, however, authorized to consider whether what the additive is supposed to do provides any benefit to society. Congress was explicit in its reports on this bill that the FDA would not be allowed to consider the societal benefits to be derived from use of the food additive in question. See, e.g., S. Rept. No. 2422, 85th Cong., 2d Sess. 7 (1958): Determination of a proper tolerance level "does not involve any judgment on the part of the Secretary of whether [the food additive's] effect results in any added 'value' to the consumer of such food or enhances the marketability from a merchandising point of view." *Accord,* H.R. Rept. No. 2284, 85th Cong., 2d Sess. (1958). (Congress thus rejected the position apparently advanced by Commissioner of Food and Drugs Larrick in 1956 that some consideration of the "benefit to the producer or consumer" should be permitted in the evaluation of food additives, Hearings Before Subcommittee of the House Interstate and Foreign Commerce Committee on H.R. 4475, etc., 84th Cong., 2d Sess. 194–95 (1956).) Therefore, under the food additive amendment, were a tolerance applicable for a substance such as DES, FDA would be barred from considering societal benefits in setting that tolerance.

(ii) *Conclusion As to Legislative History.* Congress thus did not authorize or require consideration of the socio-economic benefits of an animal drug in determining its safety. Indeed, the language adopted by Congress, having its roots in the human drug and food additive provisions of the law, clearly reflects an intention that FDA definitely not consider socio-economic benefits in making decisions on the safety of animal drugs. I thus conclude that Congress has made the determination that an animal drug that poses a risk to humans can never be considered "safe" because it provides an economic or other social benefit to society.

(b) *The Agency's Position.* The FDA has never considered the benefits of an animal drug that posed a risk to ultimate human consumers when deciding whether that drug is safe. The manufacturing parties do not contend that the agency has done so. Indeed, *Bell* v. *Goddard, supra,* which also dealt with DES—there as a drug for poultry—describes an FDA action with respect to an animal drug in which not even the proponents of the drug contended that benefits should be considered.

The manufacturing parties do quote from the preamble to regulations issued by the FDA in 1976 that deal not with animal drugs but rather with food additives. As first proposed in September of 1974, these regulations would have defined "safe" and "safety" to include consideration of, among other factors, "[t]he benefit contributed by the substance" (39 FR 34194 (September 23, 1974)). When the final regulations were issued, this consideration was deleted. In an apparent attempt to explain the agency's rationale for the original proposal, however, the preamble to the final regulation made the following statement (41 FR 53601; December 7, 1976):

> The Commissioner concludes that it is appropriate to recognize that the benefit contributed by a substance is inevitably a factor to be considered in determining whether a particular substance is "safe" (or generally recognized as "safe") for its intended use. The term "safe" is to be given its ordinary meaning, and in its common usage the term is understood to carry an assessment of benefits and risks. It is true, as the comment states, that minor food additives are not approved at levels that may present a hazard to the normal consumer. This result is required by the act because the benefit of a minor food additive is too small to justify the imposition of a known risk to normal consumers; use of such ingredient at levels that may present a hazard to the normal consumer would not be "safe." However, this result does not necessarily follow in the case of important food additives. For example, if it were found that a major food source such as meat or grain was associated with the development of chronic diseases in normal individuals, it would not necessarily follow that the food was unsafe within the meaning of the act. The ordinary understanding of the term "safe" would require some benefit-to-risk analysis in such circumstances.
>
> Another example relates to the incidence of allergic reactions to particular food ingredients. Adverse reactions caused by allergy are clearly a consideration in determining whether a food ingredient is safe. Ordinarily, the incidence of allergic reactions from a food additive cannot be considered because data and test protocols do not exist. When data exist, however, they may be considered, and an assessment of benefits and risks becomes relevant. For example, if it were determined that both a particular emulsifier and a particular fruit resulted in the same unusually high incidence of allergic reactions, one might reasonably conclude that the emulsifier was not safe but that the fruit was safe. Such conclusions would simply represent common understanding of the safety * * *
>
> The Commissioner has, however, deleted from the regulations the reference to consideration of benefits on the ground that this separate consideration is legitimately included within the concept of safety as used in the act. Furthermore, explicitly retaining the criterion of benefit in the regulations might be construed as requiring routine formal analysis of a factor that the agency will only occasionally need to take into account, because the agency's general guidelines will result in disapproval of food additives that may cause toxic effects in normal individuals.

This language is quoted in full because I am, on behalf of the FDA, disavowing it. It has never been the basis for an agency decision. As discussed, there is no justification for such a statement either in the statute itself or in its legislative history.

The manufacturing parties argue that this statement in the preamble to a regulation is an advisory opinion binding upon the agency. They cite for this proposition 21 CFR 10.85(d) (1) and (e). Subsection (d)(1), in fact, does identify the preamble to a final regulation as an advisory opinion. Subsection (e) states that an advisory opinion "obligates the agency to follow it until it is amended or revoked." An advisory opinion may, however, be amended or revoked in the **Federal Register** at any time after it has been issued (21 CFR 10.85(g)). To the extent that the language quoted above may be considered such an "advisory opinion," that opinion has been superseded (and, by virtue of 21 CFR 10.85(g), revoked) by at least one subsequent **Federal Register** statement that directly contradicts it. See 42 FR 19996 (April 15, 1977) (Saccharin and Its Salts): "The

Commissioner * * * notes that under the provisions of the law relating to food additives, FDA is not empowered to take into account the asserted benefits of any food additive in applying the basic safety standard of the act." In any case, the language cited by the manufacturing parties deals with safety in the context of GRAS substances and food additives, not in the context of new animal drugs. It thus would in no case be binding in this proceeding. Nor could it be said that the manufacturing parties have relied on the cited language or that may disavowal of that language is in any respect unfair to them.

(c) *Policy Arguments.* There are persuasive policy arguments against having an administrative agency such as the FDA make the kind of risk-benefit analysis sought by the manufacturing parties here. It may be that preliminary issues in this analysis are of the type that the FDA is qualified by experience and expertise to resolve. The agency is equipped, for instance, to evaluate calculations of the risk from a drug such as DES if the necessary data are available (they are not here). Once the risk and the benefits of an animal drug are determined, however, the ultimate issues require pure value judgments. (On the difficulty such judgments present for the administrative process and for judicial review, see Cooper, "The Role of Regulatory Agencies in Risk-Benefit Decision-Making," 33 Food, Drug, Cosmetic L. J. 755 (1978).)

It may be suggested that the agency makes risk/benefit analyses often with respect to such products as human drugs and medical devices. This suggestion is, however, incorrect. Properly understood, the agency's evaluation of, for example, a human drug is a comparison of risk to risk. The risk of using the drug is weighed against the risk of not using it. Moreover, the risks and benefits (or avoidance of other risks) are of the same type (relative to health), accrue to the same persons (patients), and are subject to a well-established scientific and professional discipline (medicine). Even so, this type of evaluation is rarely easy. Often a calculated risk of one harm must be weighed against a significantly smaller risk of a much greater harm, as with a useful drug that occasionally produces severe side effects. The factors considered are all detriments to the public's health, however, and the decision may be appropriately considered to be a medical one.

Here, however, the manufacturing parties ask the FDA to weigh a risk of cancer and other serious adverse effects against an economic benefit. Arguably, the persons at risk also receive part of the economic benefit because the meat they purchase may be available at a lower price because of the use of DES. But much of the economic benefit, as evidenced by the tenacity with which the withdrawal of the DES NADA's has been fought, goes to parties other than the consumers of the meat products of DES-treated animals.

Perhaps society is willing to expose all of its meat-consuming members to a relatively small risk of cancer and other adverse effects in order to provide a small economic benefit to those consumers and a larger economic benefit to DES producers and, potentially, users. The FDA is not, however, qualified in any particular way to make that value judgment for society. The value judgment could not be supported by a record; a record could support only factual findings, not value judgments. Nor could the value judgment be effectively reviewed by a court, which in general is limited to consideration of facts, law, and procedures. In a democratic system, the appropriate place for value judgments to be made is the legislature. Here, as discussed above, it is apparent that Congress has shouldered the responsibility for resolving this issue. It has decided that no economic benefit justifies use of an animal drug that presents an identifiable risk to the health of consumers.

The manufacturing parties also ask FDA to consider general nontherapeutic health benefits from the use of DES. Nothing in the language or legislative history of the statute or in FDA's prior interpretation or application of the statute suggests that consideration of such benefits is either required or permissible. There is nothing to suggest that Congress or FDA has ever thought that such benefits might flow from the administration of drugs to animals. Thus, it is understandable that Congress did not contemplate that FDA would consider such benefits in determining the safety of animal drugs, and that FDA has not done so.

The argument that FDA *should* consider such benefits appeals to some as a public policy but that appeal can hardly outweigh the combined force of language, legislative history, and agency practice that weighs *against* consideration of such benefits. In view of the importance of the question, I believe it should be resolved only on a record that squarely presents it. Here, as discussed in sections III(E)(2) (c) and (d), the manufacturing parties have not shown that DES presents health benefits that could outweigh its risks. The quality of the evidence in this record on health benefits is so unsatisfactory that it does not provide a sufficiently powerful policy argument for raising the legal issue. Therefore, I would rather leave the legal question open, while recognizing that it would require a very powerful showing indeed to outweigh the strong legal arguments against consideration of such benefits.

(d) *Conclusion As to Proprietary of Risk-Benefit Analysis.* The law is clear that the FDA may not consider socio-economic benfits in the determination of the safety to human beings of a new animal drug, and I am not prepared to conclude that it permits consideration of human health benefits. In order to provide as complete a record for judicial review as possible, however, I will discuss, as did the Administrative Law Judge, the evidence presented at the hearing with respect to both types of benefits.

(2) *Risk-Benefit Analysis.* It is clear that the applicant has the burden of showing that an animal drug is "safe." If a risk/benefit analysis were appropriately a part of an animal drug safety decision, the applicant would, therefore, have the burden of showing that the benefits of the drug outweigh its risks. The allocation of the burden of proof is important because the record of this proceeding is totally inadequate even to determine what the risks and benefits of DES are (or how great the risk of DES use is), much less to provide any guidance on how the weighing of risks against benefits should be accomplished.

(a) *Quantitative Risk Assessment.* Some manufacturing parties' witnesses extrapolated from the Herbst data to calculate extremely low levels of risk of human cancer in females from the ingestion of DES-contaminated meat (see M–63; M–99; M–104). (These risk calculations do not address the question of how great a risk DES poses to human males.) Other manufacturing parties' witnesses argued that there is, in effect, no risk from the present uses of DES (M–69; M–40). For the reasons discussed below, I do not regard either of these contentions as valid. In addition, I find that the data on DES are too meager to allow any risk calculation acceptable for the purpose of supporting continued approval of DES as an animal drug.

(i) *Calculations From Herbst Data.* Dr. Herbst testified that he regards risk estimates based on his data as highly suspect (G–37 at 5):

> I am informed that others have attempted to calculate and extrapolate risk estimates and "no-effect levels" in the whole United States population for DES in food using data from our Registry, but I do not believe these calculations can properly be made from our

data, nor that "no-effect levels" can be extrapolated from our epidemiological observations of effect levels.

I agree with Dr. Herbst's opinion on this issue. The manufacturing parties' risk assessments from the Herbst data merely demonstrate that the results of a risk calculation are dependent on the assumptions on which it is based.

The following assertions about the risk of DES should be read in light of the unsupported assumptions upon which they rely, i.e., that (1) the only cancer DES causes in women is vaginal adenocarcinoma in the daughters of DES exposed mothers; (2) there is a straight line dose-response for DES from the lowest DES dose that has been associated with vaginal adenocarcinoma; (3) the risk of lifetime exposure to DES is identical to the risk of exposure of the child to DES during the mother's pregnancy; and (4) we know the incidence of vaginal adenocarcinoma associated with DES exposure in utero. I will first describe the calculations made from the Herbst data and then elaborate upon my reasons for not accepting the assumptions upon which those calculations are based.

In an article entitled "Environmental Factors in the Origin of Cancer and Estimation of the Possible Hazard to Man" (M–63), the authors, Dr. H. B. Jones and Dr. A. Grendon, calculated that under "very conservative" assumptions the risk of DES-related cancer from meat consumption to the female population of the United States is 3 in 100 million. The authors then assumed that there are 4 million births per year in the United States, so that this risk is equivalent to one cancer every 8 years. Their "conservative" assumptions are as follows:

(1) A pregnant woman eats 10 oz. of beef muscle every day, except 1 day per week, in which 6 oz. of beef liver are substituted.

(2) Beef liver contains DES at a concentration of 2 ppb, and the concentration in beef muscle is 0.2 ppb.

(3) 100 DES-related cancers resulted from pregnant women receiving DES treatment who gave birth during the period 1951–1955.

(4) DES was prescribed for only 1 percent of the 10 million pregnant women during the period 1951–1955.

(5) The dose that elicited the response in each of the 100 cancer victims was 1.5 mg DES/day, the lowest dose administered to pregnant women, as reported to Dr. Herbst in his Registry.

(6) The dose-response relationship to DES is linear in the 0 to 1.5 mg DES/day range. Dr. Jones and Dr. Grendon claim that when they substitute more reasonable assumptions for the six just listed the risk of human cancer in females from the ingestion of DES-treated meat is 2 in 100 trillion (1 trillion=10^{12}), or equivalent to one cancer every 10 million years in the United States. (Id.)

Dr. Thomas H. Jukes, the author of "Diethylstilbestrol in Beef Production: What Is the Risk to Consumers?" (M–104), calculated his risk estimate in a manner similar to that of Dr. Jones and Dr. Grendon. Dr. Jukes assumed a lower daily intake of DES—1.9 nanograms (1 nanogram (ng)=10^{-9} grams=1 billionth of a gram) DES/day as compared to 100 ng DES/day resulting from assumptions (1) and (2) above. Also, in his linear extrapolation from the 1.5 mg DES/day dose level, he assumed that the risk of human cancer pregnant women receiving DES therapy was 4 in 1,000, an upper limit estimate of risk computed by Lanier, et al. (G–44 at 798). Dr. Jukes then arrived at a risk estimate of less than 5 in 1 billion from consumption of DES-treated meat, or approximately 1 cancer every 133 years in the United States (he assumes 1.5 million female births per year in the United States). In his written testimony, Dr. Jukes revises his estimate to 1 case of cancer every 380 to 3,800 years (M–99 at 10), because he substituted for the 4 in 1,000 risk estimate (of cancer to females exposed in utero to DES) the 0.14 to 1.4 in 1,000 estimate proposed by Dr. Herbst (M–26 at 47).

As Bureaus' witness Dr. Hoel stated, "the central assumptions upon which these authors based their calculations have not been validated" (G–55 at 2). My discussion of the four unsupported assumptions made by the manufacturing parties' witnesses that I regard as most important follows:

First, as the Bureaus' Dr. Condon stated, one reason for rejecting these risk calculations is the fact that "they assume that the only type of cancer risk due to DES is vaginal carcinoma because it was the only human cancer on which they based their calculations" (G–21 at 4). See also Dr. Cornfield's statement that "[b]ecause of the lack of studies of other forms of cancer in the women exposed, the human evidence [upon which the manufacturing parties' witnesses rely] cannot be used to estimate a safe dose of DES in food" (G–25 at 2). Particularly in light of the fact that animal carcinogenicity studies show that DES causes cancer in a variety of organs (see, e.g., G–47; G–84), I see no basis for the assumption that DES is associated with only this one rare type of cancer.

A second reason why the risk estimates presented by the manufacturing parties are extremely small is that they have assumed that there exists a dose-response relationship between the incidence of vaginal cancer in females and the dosage of DES administered to their mothers. Put in its simplest terms, a dose response relationship in this context means that an increase in the dosage of DES administred results in an increase in the percentage of persons who are afflicted with cancer. Thus, again to simplify the matter, if cancer were found in 1 in 1,000 persons treated with 1.5 mg of substance X, 1 in 100 persons treated with 15 mg X, and 1 in 10 persons treated with 150 mg X, a dose response would be shown. If that effect were observed, it might be valid to estimate that 0.15 mg X would cause cancer in 1 in 10,000 persons.

Another possibility, however, is that 0.015 mg (or some even lower amount) of substance X causes cancer in 1 in 1,000 persons, and that increases in dosage above that do not add appreciably to that risk. Thus, persons administered 0.015 mg X would be at the same risk as those administered 1.5 mg X or 150 mg X. The assumption that because 1.5 mg X caused one cancer in 1,000, 0.15 mg X would cause 1 cancer in 10,000, would then be incorrect.

The above example oversimplifies this question but does illustrate the problem with the assumption utilized by the manufacturing parties' witnesses. As is often true with retrospective epidemiological studies, it can not be determined from the Herbst data whether there is in fact a dose-response relationship between DES dosage and the cancers observed. As Dr. Condon noted, "no such relationship [between dose and response] has been established" (G–21 at 4). Dr. Hoel reiterated this fact (G–55 at 3):

> There is no scientific support for this assumption. The reported studies of A. L. Herbst, et al. provide no basis for constructing a dose-response relationship for the observed carcinogenic effects. Without such an established relationship, it is not valid to extrapolate these data to low levels of risk.

In general, if no dose-response relationship has been established in the observable dose range, there is no justification for extrapolating to the low dose range via a dose-response curve.

The third unsupported assumption made by the manufacturing parties' witnesses is equally likely to produce a misleading risk assessment. A proper analysis of the risks associated with DES as an animal drug should deal with low-dose, long-term (lifetime) exposure, whereas the women in Herbst's Registry faced high-dose, short-term (during

pregnancy only) exposure to DES. This fact alone invalidates any risk assessment, based on the Herbst data, of human carcinogenesis from consumption of DES-treated meat (see G–21 at 4; G–55 at 3).

A fourth, though less important, unsupported assumption by the witnesses seeking to calculate the risks of DES use is the assumption that the incidence rate of vaginal carcinoma in women exposed to DES in utero is known. As Dr. Condon noted, however, there is a long latent period for vaginal adenocarcinoma; consequently, more cases may occur as the women exposed age (G–21 at 4–5). In addition, there is no certainty that all cases of this type of cancer that resulted from use of DES have been diagnosed and reported to Dr. Herbst.

For the reasons I have discussed, I regard the risk assessments provided by the manufacturing parties to prove the safety of DES in meat as unsupported and unreliable. (Note that, in any case, these estimates say nothing about the risk of cancer posed by DES to the approximately half of the population that is male. I cannot assume, on the basis of the evidence in this record, that DES does not cause cancer in males.)

(ii) *Argument That Approved Uses of DES Present No Risk.* Some witnesses for the manufacturing parties attempted to downplay the risk of DES to humans either because it contributes very little to the total amount of endogenous estrogens or because the amount of DES ingested from meat is well below what are alleged to be no-effect levels.

Dr. Elwood V. Jensen argued that the daily consumption of DES in meat is at most 40 ng and that this amount is insignificant:

> It is my considered opinion that ingestion of 40 or even 400 ng of diethylstilbestrol per day would have no physiological significance in comparison with the 20,000 to 400,000 ng of endogenous estradiol that humans normally produce (in addition to estrone which also makes a contribution to the total estrogen level).

(M–69 at 10). As I have discussed above (section III(D)(1)), however, DES is not an endogenous estrogen, and I cannot find that its carcinogenic and other adverse effects result only from its estrogenic properties.

Dr. Nicholas H. Booth apparently assumed that DES can have no carcinogenic or other adverse effect at a level at which it does not induce a uterine response. He claimed that the no-effect level from the parenteral administration of DES is 0.29 μg/kg body weight (M–40 at 2–4) because (1) the no-effect level from estradiol is 0.166 μg/kg body weight in rats (M–49), and (2) estradiol is 1.72 times more potent than DES in mice when the effect is taken to be an alteration in the vaginal mitotic count (M–48). (The mitotic count is the proportion of cells that are in the process of cell division.) This dosage of DES is 1.5 to 3 times smaller than the 6.25 ppb dosage administered to some of the mice in the Gass study (discussed in section III (D)(2)(a) of this Decision) (M–40 at 40). If beef liver contains DES at 2 ppb, he calculated that the average daily intake of DES from meat is 3.8 ng (twice the amount of Dr. Jukes' estimate), which for a woman weighing 60 kg yields 0.063 ng DES/kg body weight (id. at 6).

Dr. Booth states that if all the DES is absorbed from the gastrointestinal (GI) tract, this amount is 4,523 times below the no-effect level of the rat that he computed (id.). Whereas if only 3 percent of the DES is absorbed from the GI tract, which he regarded as the more realistic situation, this amount (17×10^{-12} g DES/kg body weight) is 167,000 times below Dr. Booth's rat no-effect level (id.).

Dr. Booth also compared (id. at 4–5) the 0.063 mg DES/kg body weight to a no-effect level in humans, which he calculated from a study of the treatment of senile vaginitis with DES (M–50). He estimated the no-effect level for oral administration in humans to be 0.476 μg DES/kg body weight, approximately 1.5 times higher than the parenteral no-effect level in rats (M–40 at 4–5).

It must be remembered what Dr. Booth considered as effects: a uterine response in the rat, a change in the vaginal mitotic count in the rat, and a favorable reaction to the treatment of senile vaginitis in humans. Dr. Booth, in his testimony, did not even discuss his reasons for assuming that these effects correlate with either carcinogenesis or any other adverse effect associated with DES. No evidence in this record demonstrates such a correlation. See the discussion of my reasons for rejecting the argument that DES is no different from endogenous estrogens (section III(D)(1) of this Decision). Finally, the manner in which Dr. Booth combined the results from studies with different species and different methods of administration in order to calculate no-effect levels has not been justified.

I can not agree that any amount of DES, no matter how small, has been shown to be safe. On this point, my conclusion is supported by the opinion of Dr. Rauscher: "Because of the lack of data concerning the exact levels of DES which may elicit cancer in humans, we cannot say how small an amount may cause cancer nor how long that cancer will take to appear" (G–70 at 4). See also Dr. Saffiotti's testimony that "exposure to any amount of a carcinogen, however small, will contribute to the total carcinogenic effect in the population * * *" (G–80 at 6–7).

(iii) *Risk Calculations from Animal Data.* Having found that the risk calculations proffered by the manufacturing parties are invalid, I have considered whether the available data permit any reliable estimate of the risk of DES use. Dr. Hoel noted what he considered to be the only plausible alternative method for conducting a risk assessment of DES in meat (G–55 at 3):

> Estimation of cancer risks due to long-term (lifetime), low-level exposure to DES is, for the present, made only by extrapolation from lifetime toxicity studies in experimental animals.
>
> Even though such estimations require extrapolation from animals to humans, the general absence of risk data on lifetime human exposure to DES makes it necessary to use animal data.

None of the manufacturing parties' witnesses attempted such an extrapolation from animal data.

Some Bureaus' witnesses calculated from the results of the Gass study that 1 ppt DES would present a risk of less than 1 cancer in 1 million exposed (see, e.g., G–34 at 2). This calculation, even if accepted as valid, is hardly relevant to present use of DES which, the record shows, results in DES residues in edible tissues above 1 ppt. (See, generally, section III(B) of this Decision.)

As noted in the section dealing with the analytical methods for DES (II(A)(2)), this calculation is, in any case, unreliable. As discussed in that section, substances metabolize in the body, and the metabolites of a substance may be more toxic than the parent compound. Because different metabolites may be formed by different species (see, e.g., G–24 at 10416), testing of the parent substance in one species can not provide definitive information about the toxicity or carcinogenicity of that substance in other species. If, for example, DES metabolism in the body of a steer produces a carcinogenic metabolite that is not produced by DES metabolism in the mouse, the results of the Gass mouse study would not reflect that metabolite. Thus, extrapolation from the Gass study of DES could show DES to be less carcinogenic to humans than it actually is. Because the required metabolism studies of DES do not appear in the record, there is no basis either for the calculation made by the Bureaus' experts or for any calculation of the risks of present uses of DES.

(iv) *Conclusion as to Quantitative Risk Assessment.* I find that each of the risk calculations for DES proffered by

the manufacturing parties rests on unwarranted assumptions and must be rejected. The record does not provide data that make possible a reasonably well grounded calculation of the risk from the presently approved uses of DES.

(b) *Introduction to Discussion of Benefits.* The discussion that follows deals first with the contention that DES use provides "health benefits" to society by (1) decreasing the amount of fat in the human diet and (2) saving food. I then discuss the evidence in the record that DES use provides an economic benefit to society. Because the argument that one should consider the "health benefits" of an animal drug in determining its safety has some appeal, I have considered the evidence in the record regarding claimed "health benefits" with especially great care. (The manufacturing parties make passing reference to a claimed health benefit from reduction to animal waste (Manufacturing Parties' Exceptions at 178 n. *). Dr. Preston's statement that "there is potentially less animal waste" associated with DES use (M–124 at 4) is all the evidence to which I have been cited on this question and I cannot find, on the basis of that single unsupported statement, that reduction in animal waste is a health benefit associated with the use of DES.)

One factor that the manufacturing parties seem to ignore is the availability of alternatives to DES. If a claimed benefit from the use of DES is also available from a potential substitute, it is appropriate as a matter of common sense and logic to discount that benefit in determining whether the benefits of DES outweigh its risks. (This practice is followed by the Environmental Protection Agency in the risk/benefit decisions it must make, see, e.g., 44 FR 15874, 15876 (March 15, 1979) (2, 4, 5–T); 43 FR 51132, 51135 (November 2, 1978) (endrin).) The proponents of DES have provided very little information to this record about the availability of alternatives to DES.

Information about alternative growth promotants is not readily available from sources of which I could appropriately take official notice. While NADA's approved after 1969 are required to be made the subject of a published regulation, see 21 U.S.C. 360b(i), not all previously approved drugs are the subject of such regulations. Some animal drugs may, in addition, be exempt from the definition of "new animal drugs" or subject to its "grandfather" clauses, see 21 U.S.C. 321(w); Pub. L. No. 90–399, Section 108(3)(1969). Such drugs need not be covered by approved NADA's and thus would not be the subject of published regulations. Even where regulations are published, they show only that a drug is approved. They say nothing about its comparative effectiveness, cost, or availability. The components of the FDA that have first-hand knowledge about animal drugs are, of course, not available to me in making this decision.

The FDA has proposed to withdraw approval of two potential substitutes for DES, Synovex-S and Synovex-H implants, 44 FR 1463 (January 5, 1979). Those products will, of course, be available for some time until withdrawal of their approval is accomplished. Nevertheless, because the FDA is seeking to remove these growth promotants from the market, they will not be considered a factor in the DES benefits determination.

(c) *Health Benefits: Reduction in Fat.* The manufacturing parties and the pro-DES intervenors argued that the ban of DES would actually have adverse health consequences because the edible tissues of animals not fed DES contain more fat than the tissues of DES-treated animals (see Manufacturing Parties' Exceptions at 175–77). As the following discussion illustrates, the manufacturing parties have not supplied to this record sufficient data to make possible any conclusions on this point.

The question whether the ban of DES would result in significant adverse health effects to the public because of an increase in fat in the diet logically must be divided into two questions: (1) How much of a difference in fat in the human diet will cause a difference in the health of consumers? (2) How much difference in the fat consumed by human beings will result from the withdrawal of approval of the DES NADA's?

(i) *Relationship Between Fat Intake and Health.* The manufacturing parties' attempt to answer the first, and simpler, of these questions is unconvincing. They rely soley on the statement of Dr. Jukes (M–99 at 15–16) that a decrease in fat in the diet reduces human exposure to diseases such as cancer, heart disease and diabetes (Manufacturing Parties' Exceptions at 177). Dr. Jukes referred to an article (M–107) that reviews a number of epidemiological reports dealing with various cancers and their possible causes. The thesis of this review is that "over nutrition" is a prominent cause of cancer. The author, Ernest L. Wynder, suggests that the American public should consume a diet lower in calories, total fats, saturated fats, and cholesterol than its present diet. The basis for this recommendation is apparently the differing incidence of breast and colon cancer in various countries. Mr. Wynder did not testify at the hearing and was thus not subjected to cross-examination on his conclusions.

I do not disagree with the general proposition that it would be a good idea for Americans to eat leaner meat, though the record provides little support for that proposition. Nothing in the record, however, provides a basis for determining how much of a fat reduction would make a meaningful difference in the health of consumers. Without *some* basis in the record for a finding on the amount of fat reduction needed to achieve a positive effect on health, I cannot reach any conclusion about the benefit to health from fat reductions attributable to use of DES.

(ii) *Effect of Withdrawal of Approval of the DES NADA's on Fat Consumption.* This question itself involves a large number of subquestions. Logically, the difference in the amount of fat consumed would equal the amount of the difference in fat between the meat of DES-treated animals and the meat of animals that would be marketed after the ban of DES times the amount of beef that would be consumed by human consumers after a ban of DES plus or minus the amount of fat that would be consumed by humans from alternatives to beef or lamb should the ban of DES alter the consumption of those products to any significant degree.

(a) Amount of Fat Saving in Meat. Each of the factors mentioned itself depends on analysis of subfactors. Thus, the amount of the difference in fat between the meat of DES-treated animals and that of animals available to the public after a ban of DES depends on what alternatives there will be to the use of DES. It is, as a practical matter, meaningless to compare the use of DES simply to the production of cattle and sheep without DES. Producers predictably will seek to maximize their profits by turning to alternatives.

The most likely alternative to the use of DES would be the use, in its stead, of alternative growth promotants. The government's environmental impact analysis (G–116) bases its conclusions on the assumption that producers now using DES would switch to other available growth promotants. (Cf. G–115, discussed below.) The environmental impact statement (issued in 1976) assumes the use of the two Synovex products (under their chemical names—estradiol benzoate plus testosterone proprionate and estradiol benzoate plus progesterone), Ralgro by its chemical name (Zeranol), melengestrol acetate (MGA), and monensin.

A large number of alternative growth promotants are mentioned in the record. These include: Synovex-S implant (200 mg progesterone and 20 mg estradiol benzoate) (PS–15, PS–20, PS–25); Synovex-H implant (200 mg testosterone propionate and 20 mg estradiol benzoate) (PS–16, PS–44); Ralgro implant (resorcylic acid lactone), 36 mg (PS–20, PA–25, M–125 at 1419); monensin-sodium (PA–31 at 6); Rumensin (monensin) (an antibiotic) (PA–23 at 453); a feed additive consisting of microencapsulated animal fats (not approved by the FDA as of February 1976) (id.); an intravaginal device to stimulate the expression of estrus in heifers (id.; cf. M–51 at 30); estradiol 17–b (PS–12); melengestrol acetate (MGA) (PS–16, PS–44); dienestrol diacetate (PS–19); hexestrol (dihydrodiethyl-stilbestrol) (id.); coumestrol (an "isoflavonic estrogen" found in alfalfa) (PS–25); zeranol in lambs (metabolic effects) (PS–30); testosterone propionate in lambs (PS–34); chlortetracycline in lambs (id.); reserpine in lambs (id.); Smilagenin (a nonestrogenic substance) (M–125 at 1419). The record does not show that any of the above (other than those products referred to in the environmental impact statement) is or is not now available or likely to be available in the future as an alternative to DES. As discussed above, a notice of opportunity for hearing has issued for withdrawal of approval of both Synovex products (i.e., Synovex-S and Synovex-H).

DES is generally used in the raising of steers (castrated male cattle), which are easier to deal with than bulls and have, in the past, been thought to provide better tasting beef. One alternative to the use of DES is a change in cattle-raising practices. In the European countries in which DES has been banned, meat producers apparently do not castrate bull calves; thus they raise bulls rather than steers (M–64 at 24). The bulls have available, as growth promotants, natural hormones provided by their testes that are comparable to the amount of growth promotant added to steers by the administration of DES (id.). An expert witness for the intervening parties, Dr. Donald R. Gill, stated that his university had produced publications favorable to the raising of bulls (as opposed to steers), but that he personally had had bad experiences with large numbers of bulls fed in commercial feed lots (Tr. at 2006–7). Nevertheless, the raising of bulls is yet another alternative that might be utilized by cattle producers wishing to maximize the growth of their cattle if DES were banned.

The next subquestion is what will be the extent of the difference in fat consumed by the public if DES is replaced by any of the alternative growth promotants. The record has little information on this question. Data on the following alternatives do appear in the record:

No growth promotant at all—Dr. Rodney L. Preston, a manufacturing parties' witness, testified that among the positive effects of the use of DES is the production of meat with more protein and less fat, a result that he characterizes as "in harmony with proper human nutrition" (M–124 at 3). Dr. Preston made no attempt to quantify the increase in protein or reduction in fat to be expected in either cattle or sheep.

A review article by Dr. Preston states that the effect of DES on carcass composition is related to the ratio between dietary protein and dietary energy (apparently, calories). At a certain ratio, DES can be expected, he stated, to decrease the deposit of fat in the carcasses of lambs (M–125 at 1416–17). Again, no amount of decrease is given.

The Administrative Law Judge cited M–109 at 700 for the proposition that the reduction in fat content in treated steers is less than 1 percent (I.D. at 19). He apparently relied upon the estimated fat in total carcass composition reflected on Table 2 of that report. The manufacturing parties take the position, which seems to be reasonable, that the amount of fat in the muscle, as opposed to the total amount of fat in the animal, is important (Manufacturing Parties' Exceptions at 176). They go on to argue that this report, because it shows increased body fat thickness (citing M–109 at 700, 701) and no increase in overall body fat, demonstrated that DES use resulted in decreased intramuscular fat (Manufacturing Parties' Exceptions at 176).

A large number of articles detailing tests with various levels of DES were submitted to the record by the intervening parties (see, e.g., PS–16; PS–17). Review of those articles shows that DES does appear to decrease the fat content of the edible tissues of treated animals, though the amount of decrease varies with the amount of DES used, the form in which it is used, the amount and kind of feed provided to the animals and the age at which they are slaughtered. Because the studies reported involved use of DES under conditions of use different from the approved conditions, it is not possible to determine from these articles how much of a saving of fat in edible tissues occurs when DES is used in accordance with its approved uses.

MGA—DES-treated cattle are reported as having had significantly lower marbling scores than MGA-treated groups (PS–16). (The decrease in fat in the edible tissues of DES-treated animals apparently decreases what is referred to as the "marbling score." The decrease in the marbling score, in turn, decreases the Department of Agriculture grade assigned to the meat products (PS–20 and 1211; see, generally, for present USDA grading regulations, 9 CFR Part 53). Studies relevant to the fat question thus sometime speak of lowered marbling scores or lowered carcass grades.)

Dienestrol diacetate—A 1955 report states that DES-fed steers produced carcasses that were rated under federal carcass grades as slightly inferior to the carcasses from dienestrol-fed steers (and particularly inferior to control animals) (PS–19 at 332–33).

Hexestrol—The same 1955 report found that DES-fed steers produced carcasses slightly inferior in federal carcass grade to the carcasses of hexestrol-fed steers (id.).

Ralgro—One study showed that carcass grades with Ralgro treatment were similar to those resulting from DES treatment (PS–20).

Testosterone propionate—One study showed that DES treatment of lambs caused significantly lower carcass grades than treatment with testosterone propionate (PS–34).

Chlortetracycline plus reserpine—These drugs, when administered together, produced significantly higher grades of carcasses of lambs than did DES treatment (PS–34).

Bulls as alternatives to steers—Bulls are reported as having less marbling in the lean meat than DES-treated steers in one study (PS–4). In another study, bulls were compared with steers in a test in which half of the bulls and half of the steers were treated with DES (24 mg in pellets for the steers and 60 mg in pellets for the bulls). The report states that the carcasses of both the treated and the untreated steers were significantly higher in fat content than the carcasses of the untreated bulls (PS–35). A table in the study shows that the carcass grades of the treated steers were higher than the carcass grades of the untreated bulls and that the percentage of carcass fat in the treated steers was greater than the percentage of fat in the treated bulls (id. at Table 3). A subsequent evaluation of animals from this study also found that steers generally had more abundant marbling than did bulls (PS–36).

None of the cited information gives a real basis for a calculation of how much, if any, saving in the fat content of meat would result from the continued use of

DES. It appears, in fact, that if Ralgro is substituted for DES, the same fat saving (if any) would result. If bulls were raised as an alternative to treated steers, fat content would apparently be decreased. It is, in any case, not clear whether the indicators of fat content in these studies are significant in the real world. For example, if the fat on a steak is of the type that would normally be trimmed by the butcher, or by the cook or consumer prior to eating, then that fat would not have any adverse effect on the consumer. (Presumably, where the reports speak in terms of marbling, the fat in question would not normally be trimmed before consumption.)

(b) Amount of Beef and Lamb That Will Be Consumed. Another factor in the computation of the potential increase in fat in the human diet from the withdrawal of approval of the DES NADA's is, of course, the amount of beef and lamb that a human being would reasonably be expected to consume. Nothing in the record tells us how much lamb a person may be expected to consume. The CAST Report (M–51 at 26) cites a 1976 Department of Agriculture economic research service report as calculating the average consumption by Americans of beef as 2.3 pounds of "carcass weight equivalent" per person per week. Apparently, the actual amount of beef consumed would be smaller since the "carcass weight equivalent" would include the nonedible portions of the animal's carcass.

Estimates of the amount consumed were also given by manufacturing parties' witnesses seeking to compute a total risk to humans from the use of DES. See, e.g., M–63 at 261–62. They estimated the average intake of beef per day variously at 140 g and 284 g for purposes of calculation. If, as the manufacturing parties seem to argue, the withdrawal of approval of the NADA's for DES would decrease the availability of beef to the public, then the amount of beef consumed would decrease. If, as predicted by the manufacturing parties, beef prices increase when DES is no longer available, that price increase might lead to a decrease in beef consumption (M–51 at 26). A decrease in beef consumption would, of course, tend to carry with it a decrease in the consumption of beef fat. The magnitude of this decrease in overall beef consumption and its impact on total consumption of fat cannot be determined from the record. Nor does the record show how this decrease in fat would compare to the increase that the manufacturing parties project would result from discontinuance of the use of DES.

(c) Amount of Fat in Alternatives to Beef and Lamb. The record contains little information about the potential substitutions likely to be made in the diets of Americans if, in fact, the amount of beef available is decreased, or consumption is lowered due to price increases, as a result of the withdrawal of the approval of the DES NADA's. That substitutions would occur is emphasized by an intervenor's exhibit (PA–22), which is an attempt to predict the economic impact of restricting feed additives in livestock.

In a simulation dealing with the ban of DES, the authors of PA–22 calculated price effects not only in beef, but also in pork, broilers, and turkey. (The amount of lamb produced in this country is apparently so small, relative to the amounts of other meats, that it was not considered in this analysis.) The effect on the prices of these other meats caused by a decrease in availability of or rise in the price of beef assumes that the American consumer will substitute these other meat products for beef if use of DES is no longer permitted. Thus, it is important to know what the fat content of these alternative meats is. This information is not in the record. The failure to take into account the amount of fat involved in the eating of alternative meat (or other) products would presumably result in a faulty computation of the effect of a ban of DES on fat in the diet.

It is noteworthy that one manufacturing parties' exhibit states that a ban of DES, if it decreases the amount of beef consumed, will lead to consumption, in the alternative, of cereal products (M–51 at 26). Presumably, this change would result in less total fat intake in the average diet.

(iii) *Conclusion as to Claimed Health Benefit From Decreased Consumption of Fat.* The Administrative Law Judge found, in essence, that the manufacturing parties had failed in their burden of showing benefits of DES. An analysis of the claim that DES has a health benefit in reduction of fat shows that the Administrative Law Judge's conclusion with respect to that claim was correct. The record simply fails to support the contention that DES provides a health benefit by reducing dietary intake of fat.

(d) *Health Benefit: Feed Saving.* The manufacturing parties cite as a second health benefit of DES the saving of food that results from the feed efficiency associated with the drug (Manufacturing Parties' Exceptions at 177). The manufacturing parties rely on the testimony of Dr. Jukes that the feed-saving value of DES is estimated (he did not say by whom) at 7.7 billion pounds annually and as being equivalent to 3 million to 4 million acres of corn (M–99 at 17–18). Dr. Jukes then stated that a yield of 150 to 175 bushels of corn per acre per year would supply an additional ration of 500 calories per day per person to 80 percent of the world's hungry people (id.). (Dr. Jukes apparently assumed that the saving in animal feed grain would result in the production of more human food grains.)

Dr. Jukes' argument is curious, since presumably the amount of feed that DES saves is presently available. Thus, if this food is not being used at this point to supply the additional calories to 80 percent of the world's hungry people, there is not much to be said for the argument that DES use should be continued so that this excess food capacity will be available.

The Administrative Law Judge noted that any prospective grain saving from DES would be of less importance because there is presently no grain shortage in the United States, where the grain savings would, of course, be generated. As the manufacturing parties argued, the question properly is whether, if DES were no longer available, there would be a grain shortage. In fact, the testimony cited by Judge Davidson supports the proposition that, at the time of cross-examination, there was a surplus of grains (Tr. at 2014). Because the record does not reveal whether any increase in grain consumption associated with the unavailability of DES would be greater than any present surplus of grain, it has not been shown that a ban of DES, even if it did increase grain consumption, would lead to shortage.

Evidence in the record suggests that the unavailability of DES might not have a very significant effect on the fluctuating grain situation. A Department of Agriculture Economic Research Service report (PA–28) that is undated but utilizes 1969 figures notes that cattle finishing (the stage at which DES is most often used) accounts for only 16 percent of all feed grain use (id. at vi). (Thus, even if the unavailability of DES increased grain consumption in feed lots to some extent, the effect on the total grain supply would not necessarily be great.)

This report's projection of the different possible effects of a DES ban illustrates the difficulty involved in making this type of estimate. The report, which assumes the absence of alternative growth promotants, considers the effects of three possible results of the ban: (1) feeding the same number of cattle for the same length of time (and thus producing less meat per animal); (2) feeding the same number of

cattle for longer periods; and (3) feeding a larger number of cattle for the same period (id. at v). The report acknowledges that the actual result would probably be some combination of these options (id.). (Since this report was apparently prepared without the benefit of data from the ban of DES in the early 1970's, its projections are necessarily more speculative than those discussed below in the economic benefits section.)

The report projects that option (1) would result in a reduction in feed consumption of 2 percent (id. at vi) (feed consumption would be reduced because untreated cattle consume less feed per day than DES-treated cattle); option (2) would result in a significant increase in feed consumption (no percentage is given) (id. at vii); option (3) would result in a 2.1 percent increase in feed consumption (id.). The report then states that option (2) (in which the ban of DES results in an increase in feed consumption over consumption associated with DES treatment of cattle) would result in a $100 million saving to the economy because the increase in feed consumption would reduce the costs of the feed grain program! (Id.)

A manufacturing parties' document—Council for Agricultural Science and Technology, *Hormonally Active Substances in Foods: A Safety Evaluation*, Report No. 66 (March, 1977) (CAST Report) (M–51 at 26)—notes that the ban of DES, assuming it results in a decrease in efficiency of feed utilization in beef production, would be expected to have little effect on the release of grain for world trade. The report notes that, as feed efficiency increases, the price of beef decreases which, in turn, encourages more consumption of beef and, thus, more production, followed by the use of more feed to produce that beef. When efficiency decreases (as it would in the absence of DES and other growth promotants), the price of beef rises, consumption decreases, production of beef decreases and more grain is available. On the other hand, presumably any consumption decrease will be associated with a turn by consumers to other meats and to cereal grains. This increased consumption of cereal grains might itself have some effect on food grain availability. The CAST Report does not discuss this possibility, however.

The manufacturing parties do not present evidence on the loss of grain, and on the effects of that loss, during the 1974 ban of DES. Perhaps more important, moreover, the manufacturing parties do not present evidence of the amount of grain loss that could be expected if, as would be logical, beef producers turn to other growth promotants when DES is no longer available.

It is simply not possible from the evidence in this record to determine whether and to what extent the withdrawal of approval of the DES NADA's will affect the availability of feed grains. Even if there were a decrease in the availability of feed grains, it is not possible to determine whether and to what extent that decrease would result in a decrease in food that would otherwise be made available to, and would provide a health benefit to, human beings.

(e) *Economic Benefits.* The nonparty participants state their position that DES produces an economic benefit boldly: "If DES really has no value, then as a practical matter *it simply won't be used*" (emphasis in original) (Intervenors' Exceptions at 5). This argument has a strong initial appeal. DES, without question, enjoys wide use, presumably by people who believe it is in their economic self-interest to use the drug. Yet the FDA's experience with human drugs counsels skepticism toward a claim that something is true because most people believe it to be true. (Many such drugs have been widely used for years, only to be found later, upon objective test, to be worthless.)

The record in this proceeding contains little support for the proposition that DES provides a significant economic benefit to society that would not be provided by available alternative growth promotants. More important, the record provides no reliable basis for determining how great the economic benefit of DES, if any, is. Nor does the record make possible a decision as to who receives any economic benefit associated with the use of DES as an animal drug.

As I have discussed in section III(E)(1), I am not authorized by statute to decide that an animal drug is "safe" because the economic value of that drug is more important to society than the risk of cancer it poses to consumers. If I were so authorized, I could not make a responsible decision without substantial evidence that DES does provide an economic benefit, and without substantial evidence showing how great that benefit is and to whom it accrues.

The proponents of DES use have done a very poor job of providing information to this record on this issue. No expert economist testified, though the task of forecasting the economic effects of the unavailability of DES is complex. Despite the fact that DES been removed from the market previously (premixes for more than a year, implants for 9 months), the proponents of DES use have presented no careful analysis of the economic results of that action. As discussed above, the manufacturing parties have the burden of proof on the risk/benefit issue, if that issue is appropriately a part of this proceeding at all.

(i) *Does DES Provide an Economic Benefit?* Without question, DES provides an economic benefit to the drug companies that make and sell it. Presumably even if I were required to make a risk/benefit analysis of DES, I could safely disregard that benefit. The discussion that follows thus considers the evidence in the record that use of DES as an animal drug provides economic benefits to other segments of society.

To determine correctly whether the withdrawal of approval of the DES NADA's will result in an economic cost to society, I must know whether DES improves the efficiency of cattle and sheep production more than would the alternatives to which DES users would turn if DES were not available. To make my decision meaningful, however, I must also know to what extent other growth promotants will be available to replace DES and whether (and to what extent) such alternatives will be more expensive than DES.

The evidence in the record on the relative efficiency of DES and alternatives is not sufficiently clear for me to make any findings. A multitude of studies in the record (almost all submitted by the intervenors) show that DES (1) increases the rate of weight gain of steers and (2) decreases the amount of feed needed, and the amount of feed lot time needed, for fattening. It was, presumably, the demonstrated effectiveness of DES as a growth promotant that justified its continued approval after the 1962 amendments to the drug laws required that drugs be shown to be effective as well as safe. (There is no issue in this proceeding with respect to the evidence of DES's effectiveness except as that issue may affect the issue of benefits and (if benefits are relevant to safety) ultimately the issue of safety.) Thus, when compared to the use of no growth promotant at all, the use of DES has been shown to result in an economic benefit to cattle and sheep producers.

The more difficult question is whether, and to what extent, DES presents a significant economic benefit compared to the likely substitutes for it. The many substitute growth promotants mentioned in the record have been noted previously in section III(E)(1)(2)(c)(i). Tests included in the record comparing substitutes to DES provide sometimes

conflicting evidence on this question. Test conditions vary from actual conditions of use. No expert testimony was provided interpreting the results of these tests. For these reasons, I cannot make any findings on the basis of them.

Because the FDA is proposing to withdraw approval of the NADA's for Synovex-S and Synovex-H, I do not consider those drugs to be substitutes for DES. The tests comparing them to DES are thus not discussed here. Test results are reported for the following other potential substitutes:

Ralgro implant—In a test reported in 1975, a 15 mg DES implant was compared to a 36 mg Ralgro (resorcylic acid lactone) implant (PS–20). The Ralgro implant produced a slightly lower daily weight gain in a test with steers weighing from 309 to 352 kg, while requiring less feed per kilogram of gain than the 15 mg DES implant (id.). In a second test involving steers weighing 192 kg, the Ralgro implant caused slightly higher average daily gain than the DES implant and required slightly less food per kg of gain (id.).

In an unpublished report, a 36 mg Ralgro implant was found to result in a gain of about half the amount achieved with a 36 mg DES implant (PA–25). Essentially no improvement in cost of gain over controls was obtained with Ralgro (id.).

In a study reported in 1973, a 36mg Ralgro implant produced an average daily gain in steer calves slightly, but not significantly, greater than 10 mg oral DES and a 12 mg DES implant, with a feed-to-gain ratio essentially equivalent to that of the DES treatments (PS–12).

Estradiol 17-b—Estradiol 17-b, a natural estrogen, has been tested against various doses of DES under a variety of conditions (PS–12). In some of these, the Estradiol 17-b has been shown to be as good as or better than DES. In others it was not as good.

Melengestrol acetate (MGA)—Although neither DES nor MGA influenced the growth of steers and heifers during the hot summer months in feed lots in Arizona, a 24 mg DES implant increased the gains of steers significantly more than did MGA administered at the rate of 4 mg per animal daily (PS–44). On the other hand, heifers treated with MGA had significantly greater daily gains than control or DES treated heifers.

Dienestrol diacetate—A study reported in 1955 compared 10 mg DES with 10 mg dienestrol and found that dienestrol-fed steers gained "slightly less rapidly" than DES-fed steers, though their gains were significantly greater than the gains of the control animals (PS–19).

Testosterone Propionate—10 mg implants of this androgen in lambs produced average daily gains only slightly less good than those produced by 3 and 6 mg DES implants, but required more food per pound of gain than DES implants (PS–34).

Reserpine—This substance, when fed at 0.25 mg and 0.50 mg in lambs, produced average daily gains lower than DES implants or DES fed orally, with the higher amount of reserpine producing the worst results (PS–34). The feed per pound of gain was also increased over the DES treatments (id.).

Raising bulls instead of steers—As noted above in section III(E)(2)(c)(ii)(a), Dr. Donald R. Gill, a witness for the intervenors, testified concerning a suggestion that DES would be unnecessary if beef cattle were raised as bulls rather than steers. Dr. Gill testified that the problem with this suggestion was that bull feeding would require putting calves of 6 to 7 months of age on high grain rations. Apparently, under the present system such calves are grazed for from 6 months to a year before being taken to the feed lots and fed for the last 2 to 3 months of their life (see Tr. at 2013). Thus, according to Dr. Gill, shifting to the production of bulls would mean that grazing land presently used would cease to be useful and more grain would be consumed. Dr. Gill also noted that the consumption of grain, in a country where the government purchases grain surpluses, can be good one year and bad the next. He stated that on November 2, 1977, the date of cross-examination: "I was at a conference with USDA people last week, and with our surpluses it's becoming good again to use up grain" (Tr. at 2014). Dr. Gill further stated his opinion that the feeding of large groups of mature bulls (50 or more in 1 pen) presents a very serious management problem and will not work to the benefit of either producer or consumer (PA–32 at 2).

There is no reliable evidence in this record upon which to base conclusions about either the availability of substitutes for DES or the relative cost of such substitutes. Presumably, in the absence of supply problems, market forces would make substitutes more widely available if DES were banned. Economies of scale might bring prices of these substitutes down from their present levels. Alternatively, the increased demand might drive prices up if supplies were constrained. New products currently under development might also affect the economic consequences of a ban of DES. Nothing in this record provides a basis for any findings on these questions.

(ii) *How Great is the Benefit?* The calculations by the manufacturing parties and pro-DES intervenors of the actual economic effect of a ban of DES are, in each case, unsupported. In addition, these calculations appear to be based on the assumption that the alternative to DES is the use of no growth promotant at all. No other evidence in the record provides a basis for a realistic calculation of the "real world" economic effects, if any, on society of the withdrawal of approval of the DES NADA's.

Dr. Jukes is cited by the manufacturing parties as testifying that the economic benefit to the American economy of DES is some $800 million to $1 billion annually (Manufacturing Parties' Exceptions at 180). The testimony cited bases its computations upon phrases attributed to Senator Kennedy and Representative Fountain, computing the cost respectively as $4 to $5 per person per year and $3.85 per person per year (M–99 at 17). No evidence is presented that would support the per capita estimates.

Dr. Preston, a manufacturing parties' witness, testified that "various estimates indicate that $8–15 are returned for every dollar invested in the use of DES in cattle and sheep production" (M–124 at 4). Dr. Preston was very vague, on cross-examination, in explaining who made the estimates and how they were arrived at (Tr. at 1620–21). He did say that the savings was based upon feed efficiency and the overhead, interest, "death loss" and other components of cost saved by the decrease in the time in the feed lot necessary for DES-treated cattle (id.).

Intervenors' witness Dr. Gill estimated the value of the use of DES to feeders as $24 per head (PA–32 at 2). This figure was apparently calculated on the basis of savings in feed and feeding time resulting from the use of DES (see Tr. at 2008–09). Dr. Gill could not cite the studies upon which he relied for the proposition that pasture-fed steers treated with DES improved their gain by an average 22.46 percent. Although he offered to try to find these studies and produce them, they were not available for his cross-examination (Tr. at 2011) and have not been identified for the record.

An only slightly more helpful appraisal of the economic benefit of DES may be found in an inflation impact statement for the withdrawal of approval of the DES NADA's submitted by the Bureaus (G–115). The report is dated January 1976. It estimated the total cost impact of removing DES from

the market at $659 million during the first year (id. at 5). The bases for this evaluation are open to question.

It is estimated that feed lot producers of cattle will experience increased costs of $156 million (id.). Of this, approximately $4 million will be incurred by the producers of DES-implanted cattle as costs for changing to alternative estrogenic growth promotants (id.). The report stated that in 1974, 65 percent of fed steers received implants, of which 3.9 million of 10.9 million (approximately 36 percent) were using DES implants (id. at 4). The remainder were, it states using Synovex and Ralgro implants (id.). The assumption that those producers using DES implants would change over to the alternative estrogenic implants is based upon experience with the previous FDA ban of DES implants.

One hundred fifty-two million dollars in increased costs is allotted to the producers who use oral DES and represents the cost of increasing feed to provide the same amount of growth in untreated steers as would occcur with DES (id. at 4–5). The report states that 25 percent of the steers slaughtered in 1974 were receiving oral DES (id. at 3).

The assumption that producers feeding oral DES would switch to nonmedicated feed is also based upon experience with the previous ban of DES (id. at 4). The report notes, however, that the failure of producers to switch from oral DES to non-DES implants during the previous ban may be attributed to a shortage of supply of the non-DES implants (id. at 5). The allocation of cost—$152 million for the 25 percent of the steers that use DES orally and $4 million for the approximately 22 percent of steers that use DES implants (36 percent of 65 percent)—suggests that it would make economic sense for those using DES in feed simply to change over to non-DES implants. The report notes that in the opinion of a consulting animal scientist it would be no problem for a feed lot producer to make such a switch (id.).

The remainder of the estimated $659 million cost is allocated to an increase in the retail cost of meat by 2.2¢ per pound. This increased cost of $503 million is based upon an estimated decrease in the availability of meat. This estimate in turn is based, again, on no change-over from DES in feed to non-DES implants. It also assumes that meat producers do not, as they in fact do, decrease herd sizes when prices go down and increase herd sizes when they rise (cf. M–51 at 26).

(A witness for the intervenors, John W. Algeo, in fact testified concerning the "cattle cycle." He stated that at the time of his testimony, September 13, 1977, that cycle was coming to a turning point after years of over-supply and three years of liquidation (PA–29 at 4). He argued that lower production costs eventually mean lower meat costs but admitted that "this is at times hard to see due to the daily and cyclical market fluctuations" (id.). Mr. Algeo's testimony was withdrawn on the day on which he was to have been cross-examined (Tr. at 210), and I do not rely upon that testimony.)

An article by Mann and Paulsen, entitled "Economic Impact of Restricting Feed-Additives in Livestock and Poultry Production" (PA–22), apparently published in *Amer. J. Agr. Econ.* in February 1976, was submitted by intervenors. This article, using simulation techniques, attempted to predict the rise in wholesale prices that would be the result of bans of antibiotics and DES. This simulation takes into account the effect on prices of alternative meats should beef production be cut by the unavailability of DES. In a simulation dealing only with the unavailability of DES, the authors calculated that meat prices for beef, pork, broilers, and turkey would rise substantially and remain high for the five year period for which calculations were made.

The authors also performed a simulation, however, that takes into account the likelihood of technology developing replacements for DES and antibiotics. (The simulation assumed that it would take a year for replacement therapy to be available, though it acknowledged the present availability of Synovex and Ralgro.) In this assessment, the authors conclude that by the fourth year prices will actually fall below the first year baseline in each meat category after the ban of both antibiotics and DES (PA–22 at 51). This reduction in prices was predicted to result from the stimulation to supply provided by the increased prices during the ban, which would, as the cycle reached the point of slight over-supply, reduce prices.

Neither the authors of this report nor any other expert economist trained to forecast the likely effect of such actions as the withdrawal of approval of the DES NADA's was presented as a witness at the hearing. No attempt was made by any witness to analyze the real world economic effects of the lack of availability of DES and the availability of alternatives to it.

Moreover, the CAST Report contains a statement that would seem to contradict the manufacturing parties' position:

> A ban of DES at present would probably have little effect on the beef-cattle industry as long as substitutes, which have similar effects, remain available (Cothern, 1974, 1975, 1975a). Meanwhile, a ban on DES would permit the export of fed beef from the United States to countries such as Canada that now forbid its import because they ban DES and we do not.

(M–51 at 29.) The report also cites calculations of the estimated changes in wholesale prices of meats following withdrawal of approval of the DES NADA's with no substitutes being available. Because, however, there are substitutes, this information is of questionable relevance.

The CAST Report, in considering the possible effect of the removal of DES from the market "without replacement" on the availability of grains for export to developing countries, concludes that the "quantitative effects [of the ban of DES] would probably be too small to detect among the numerous other factors that influence prices of beef cattle and feed grains" (id. at 6).

This record simply lacks information sufficient to allow me to make any determination about the extent of the economic costs, if any, of the withdrawal of approval of the DES NADA's.

(iii) *Costs of Use of DES.* The Administrative Law Judge noted that a consideration of the possible economic benefits of DES must include consideration of the economic costs of such use (I.D. at 21). He cited the economic costs of "bulling" (id.). The term "bulling" or "riding" refers to steers mounting one another (I.D. at 21, n. 15). Although bulling occurs in feedlots without DES-implanted or fed cattle, the incidence of this activity increases where DES implants are used (Tr. at 2067). The only witness testifying on this subject, Dr. Flack, gave his opinion that DES feeding, as opposed to implantation, does not lead to increased bulling (Tr. at 2068).

The steers apparently can harm or kill one another during bulling. The record does not state the extent to which this activity increases, or the extent of harm to the cattle, when DES is administered. Nor does it provide information sufficient to be a basis for any conclusion about the economic costs associated with bulling.

The Administrative Law Judge also included in the economic costs of the use of DES a greater incidence of liver abscesses associated with that use. There is little information in the record about how much greater this incidence is in actual practice. The intervenors' Dr. Flack testified that livers of cattle are valued at approximately $2.50 per head

(Tr. at 2061). I cannot, however, on this record fairly estimate the cost to DES users and the economy resulting from the loss of livers abscessed because of use of DES.

One cost (or reduction in benefit) associated with DES-use that was not discussed by the Administrative Law Judge necessarily follows from the manufacturing parties' argument that DES-treated beef produces less marbling and, thus, a lower Department of Agriculture grade, than untreated beef. It is common knowledge that higher grade beef is more expensive than lower grade beef. If there is a significant difference, then meat producers pay a cost (or reduction in benefit) in lost profits resulting from use of DES.

(iv) *Conclusion As to Economic Benefits.* Again, the Administrative Law Judge's conclusion that the manufacturing parties have failed to show the economic benefit of DES is justified. Neither the manufacturing parties nor the intervenors provided information on the basis of which I can determine (1) the difference, if any, between the economic benefits of using DES and the economic benefits of using other growth promotants (or even what growth promotants are available), (2) the likely cost or savings from any changes in consumer selection of foods that might result from action with respect to DES, or (3) the costs that might be saved by the withdrawal of approval of the DES NADA's.

There is some credible evidence that the withdrawal of approval of the DES NADA's would cause little economic harm to the public and to the beef-cattle industry beyond the cost of transition from the use of DES to other products (cf. M–51 at 26). The transition cost itself may be lessened because of the way in which events have proceeded. The Administrative Law Judge's decision has put the industry, including the manufacturers of alternatives to DES, on notice that withdrawal of approval of the DES NADA's is likely. Presumably, the manufacturers of alternatives have been readying themselves to increase production when the withdrawal becomes final.

If there were no alternative growth promotants for beef and sheep, DES would provide some economic benefit, unquantifiable on this record, to society. In light of the availability of alternatives to DES, however, the manufacturing parties have not shown that the withdrawal of the DES NADA's would result in the loss to society of significant economic benefits.

Manufacturing parties argue that they have no "special burden to prove a point that the Bureaus have already conceded" in the inflation impact statement (Manufacturing Parties' Exceptions at 180). I do not agree that the Bureaus have conceded that the withdrawal of the DES NADA's will have the total economic impact stated in the inflation impact statement. That statement itself states that one of the pivotal assumptions upon which it relies, that producers using DES in feed will not switch to non-DES implants, may not be valid (G–115 at 5). In addition, that statement was a projection based on the economic situation in the beef cattle industry in 1976. As the Bureaus argue (Bureau's Brief at 144), conditions have changed since the issuance of that document. It would thus be unrealistic for me to rely upon the inflation impact statement as a projection of the economic costs of withdrawing approval of the DES NADA's.

Even accepting the manufacturing parties' position on this issue, I could not find that a saving of $659 million in the first year after withdrawal (projected by the impact statement) outweighs the risk of cancer associated with the continued use of DES. Even the manufacturing parties' Dr. Jukes stated his agreement with the proposition that no saving in meat prices can justify a real risk of cancer in the food Americans eat (Tr. at 2183–84). Some would argue that this amount of money, if put, for example, into cancer research, would result in a saving of more lives than would the ban of DES (see, e.g., M–99 at 17). There is, however, no showing that there is any relationship between the alleged savings of costs because of the use of DES and the funding of cancer research. In fact, there is clearly no such relationship.

(F) Summary of Safety Clause Issue

Evidence in the record from radiotracer studies and the Department of Agriculture residue monitoring program provides independent bases for the conclusion that approved uses the DES result in residues of DES and/or its conjugates in edible tissues of treated animals (see section III(B)). Animal and human cancer data demonstrate that DES is a carcinogen, and that there is no identifiable no-effect level for its carcinogenicity (section III(D)(1) and (2)). Evidence in the record raises but fails to resolve serious questios about the potential teratogenicity and mutagenicity of DES, and there is no demonstrated no-effect level for DES for these adverse effects (section III(D)(3)). Because the conjugates of molecules often retain the characteristics of the unconjugated molecule, and because conjugates of DES hydrolyze to DES in the human body, safety problems with DES itself must also be attributed to DES conjugates (section III(C)).

Risk-benefit analysis is not appropriate in determining the safety of an animal drug that poses a risk to humans (section III(E)(1)). Such an analysis has been attempted here nevertheless (section III(E)(2)). The proponents of the use of DES have the burden of showing that the benefits of DES outweigh its risks (id.). They have not, in this record, provided an adequate basis for determining either the risks of DES or the benefits, if any, that it provides to society (id.).

Withdrawal of approval of the DES NADA's is thus required on the basis of the so-called "safety clause" of 21 U.S.C. 360b(e)(1)(B) (as well as on the basis of the Delaney Clause discussed in section II of the Decision).

IV. Liver Discard as an Alternative Condition of Use

The manufacturing parties note (Manufacturing Parties' Exceptions at 186) that the Court of Appeals in *Hess & Clark* stated that "the FDA might restrict such consumption [of any DES residue] by a ban on sale of liver, the only food material in which any residues have been detected" (footnote omitted), 495 F. 2d at 994. As discussed above (section III(B)(1)) with respect to the manufacturing parties' contention that the NADA's for DES as a feed additive should be judged as if they provided for 14-day withdrawal periods, the statute is clear that I must consider the conditions of use that were originally approved. Thus, a change in conditions of use to require liver discard would be proper only if the manufacturing parties had sought to amend their NADA's.

In seeking such an amendment, the applicants would have the burden of showing their product to be safe in the first instance. In a withdrawal proceeding, an applicant's interest in the status quo outweighs the public interest to the extent that the Bureaus seeking withdrawal have the initial burden, discussed above, of coming forward with evidence warranting that withdrawal. When an applicant seeks approval for a change in the NADA, that burden on the Bureaus no longer exists.

I have, however, considered the question whether approval of the DES NADA's would still have to be withdrawn if they required as they now do not, the discard of all livers.

The *Hess & Clark* Court's understanding that livers were the only food material in which DES residues had been detected is not correct. DES residues have been reported by the

Department of Agriculture only in livers (G–58 at 2). That Department, however, only analyzes livers (G–94 at 3). As noted in section III(B)(2) of this Decision, DES residues were found in edible tissues other than liver, e.g., kidneys and tongues, in radio-tracer studies (see G–2; G–5; G–76 at 5; cf. G–79) of both feeding and implantation of DES.

The manufacturing parties, however, focus on the question of whether DES residues have been found in muscle tissues. As discussed above in section III(B)(2), radioactivity that may be attributable to DES residues has been found in the muscle tissue of steers 10 days after dosing with radiolabeled DES (G–2 at 1190, Table 4) and 120 days after implantation with radiolabeled DES (G–1 at 4; G–5 at 535, Table 2). The manufacturing parties' criticisms of these results, which are at very low levels, are discussed above (see section III(B)(2)).

More important than these findings is the fact that in the muscle of animals tested at less than approved withdrawal times, DES residues were observed in amounts significantly less than those found in the animals' livers. In light of that fact, I conclude that evidence that DES has been detected after use of DES animal drugs under their approved conditions of use in cattle's livers (and other organs) is an indication that DES exists, in smaller (perhaps undetectable) amounts, in muscle tissue. See also M–63 at 261, citing Goldhammer, G. S., Government Operations—Part I (1971) at 70 for the proposition that the concentration of DES in liver is ten times that in beef muscle.

I find that the record supports the conclusion that use of DES results in DES residues in edible tissues other than liver. It follows from this finding that it has been shown that use of the DES animal drugs, even with the restriction that the livers of DES-treated animals (Or that any combination of the edible tissues of such animals) be discarded, has not been shown to be safe. Therefore, even if the DES NADA's contained the liver-discard condition of use, approval would be withdrawn pursuant to the "safety clause" of 21 U.S.C. 360(e)(1)(B).

My analysis of the Delaney Clause issue would also not change. The approved or proposed analytical methods would be no more acceptable if the NADA's provided for liver discard. On that basis, withdrawal would still be required by the statute.

(The intervenors assert that liver tissues containing substantial quantities of DES are not "edible tissues" within the meaning of the Wholesome Meat Act, 21 U.S.C. 601 et seq. (Intervenors' Exceptions at 2). It is unclear what point they seek to make. If they are arguing that USDA will automatically remove from the market tissues with DES residues, I reject that argument. As discussed above (section II(A)), there is no analytical method available by which USDA could assure that meat does not contain DES residues at levels not shown to be safe. If they are arguing that no method can ever detect DES residues in edible tissues, see 21 U.S.C. 360b(d)(1)(H), because any tissue that contains a residue is not edible, I reject that argument as absurd.)

V. Need for an Environmental Impact Statement

The National Environmental Policy Act, 42 U.S.C. 4322(c), requires the preparation of an environmental impact statement for "major Federal actions significantly affecting the quality of the human environment, * * *" The Bureaus, in an "environmental impact analysis report and assessment," issued in October of 1976 (prior to issuance of the notice of hearing), found that the ban of DES would not constitute an action "significantly affecting the quality of the human environment" (G–116). The Bureaus thus concluded that no detailed environmental impact statement need be prepared. The basis for the Bureaus' conclusion was the finding that meat producers will simply turn to available alternative growth promotants if DES is no longer available. The report refers specifically to estradiol benzoate plus testosterone propionate (Synovex-H), estradiol benzoate plus progesterone (Synovex-S), zeranol (Ralgro), melengestrol acetate (MGA), and monensin (Rumensin).

It is appropriate, under the statute, for an agency to determine that its proposed action does not create the kind of significant environmental impact that would justify a full environmental impact statement. That decision must be based upon a careful consideration of the question, including consideration of courses of action that are alternatives to the action proposed, *Trinity Episcopal School Corp.* v. *Romney,* 523 F.2d 88, 92–93 (2 Cir. 1975). The Bureaus' statement is quite detailed, has a bibliography listing 21 articles and books, and does consider the alternatives to the withdrawal of approval of the DES NADA's.

The most important finding of the report is, of course, that users of DES will predictably turn to alternative growth promotants. The report bases this conclusion on experience during the period when approval of the DES NADA's was withdrawn previously before being reinstated by court order. The report notes that the alternative drugs to which it refers are approved by the FDA for use. No one disputed, at the hearing, the Bureaus' assertion that alternatives are available.

Intervenors' witnesses did, however, raise questions about reliance upon the availability of two alternative growth promotants. First, an intervenors' witness noted that the FDA is seeking to withdraw approval of the Synovex products (PA–33 at 5). The problem posed by the proposed withdrawal of approval of the Synovex products is discussed above in the benefits section. The agency was not proposing to withdraw approval of these drugs at the time the Bureaus' decision that an environmental impact statement was unnecessary was made. Because alternative growth promotants such as Ralgro are still available, I conclude that the proposed action with respect to Synovex does not invalidate the decision that the withdrawal of approval of the DES NADA's will not significantly affect the quality of the human environment.

Another intervenors' witness argues that the fact that monensin can be used either concurrently with DES therapy or by itself means that monensin is not properly a replacement for DES (PA–31 at 6). The Bureaus do not contest the assertion that monensin is additive to DES treatment and that, for that reason, monensin should not be considered a substitute for DES for those now using the two drugs concurrently. As a practical matter, on the other hand, cattle feeders who are content to use only one growth promotant may well begin to use monensin when DES is banned.

The preparation of the environmental impact analysis report by the Bureaus before the hearing commenced was the correct procedure, see *Calvert Cliffs' Coordinating Committee* v. *Atomic Energy Commission,* 449 F.2d 1109, 1117–18 (D.C. Cir. 1971). The manufacturing parties argue that they were denied a fair hearing on the environmental impact issues because the Bureaus did not present a witness to stand cross-examination on the environmental impact analysis. The courts have not gone so far as to require that the authors of the analysis be presented for cross-examination. Rather, the requirement is that the analysis (or statement) be available so that the parties are "given the opportunity to cross-examine * * * witnesses in light of the statement," *Greene County Planning Board* v. *FPC,* 455 F.2d 412, 422, (2d Cir. 1972).

The manufacturing parties argue that the economic and public health effects of the ban of DES, discussed above, demonstrate that the ban would be a major federal action significantly affecting the quality of the human environment (Manufacturing Parties' Exceptions at 184). The manufacturing parties do not explain how loss of the claimed economic benefits of DES would constitute an effect on the quality of the human environment. The Bureaus' analysis did consider the effect that the ban would have on the availability of feed (G–116 at 11). The analysis did not consider the effect of the ban on human intake of fat.

An increase in fat intake is not an environmental effect to be considered in an environmental assessment. See *Calorie Control Council, Inc.* v. *DHEW,* No. 77–0776, slip op. at 5–6 (D. D.C. September 9, 1977), *remanded on other grounds* (D.C. Cir. September 22, 1978) (health effects of saccharin ban not cognizable under environmental law); cf. *Breckinridge* v. *Rumsfeld,* 537 F. 2d 864, 866 (6th Cir. 1976); *National Ass'n of Gov't Employees* v. *Rumsfeld,* 413 F. Supp. 1224, 1229 (D. D.C. 1976). In any case, the fat question is unusual enough that it is not logical that it would have been raised in the initial analysis. In fact, in light of the evidence in this record, I consider this issue as bordering on the frivolous. I conclude that the full discussion of the issue in this opinion satisfies the statute's intent that all environmental issues be considered before action of this type is taken.

The manufacturing parties point out that although the Administrative Law Judge found that the withdrawal of DES from the market would not significantly affect the quality of the human environmenmt, he did not discuss this issue specifically in his opinion. (The manufacturing parties themselves devote only two and a half of the 217 pages of their exceptions to this issue.) I have, however, considered carefully the possibility that the withdrawal of approval of the DES NADA's will affect the human environment. This discussion, together with the applicable segments of the risk/benefit analysis, constitutes my decision on this issue.

I conclude that withdrawal of approval of the DES NADA's will not significantly affect the quality of the human environment because DES will be replaced by alternative growth promotants. Therefore, the Bureaus' decision not to file a complete environmental impact statement for the withdrawal of approval of the DES NADA's was correct.

VI. Exceptions to Evidentiary Rulings

Both the manufacturing parties and the Bureaus have filed exceptions to certain evidentiary rulings by the Administrative Law Judge in the course of the hearing. In the interest of removing any possible cause for remand of this hearing from a reviewing court due to evidentiary rulings, I have considered those evidentiary submissions by the manufacturing parties that were excluded from the record, whether or not I have concluded that those exclusion were proper.

I have relied upon certain Bureaus' evidence that the manufacturing parties argue should be excluded. I have, however, reviewed the record carefully to determine whether reversal of any evidentiary ruling with respect to such evidence would change my decisions on the issued presented by this hearing. Thus, the following discussion considers, in each instance in which I uphold the refusal to exclude Bureaus' evidence, whether excluding that evidence would alter my conclusions in any respect. As will be apparent, even if all evidence that the manufacturing parties seek to exclude were in fact excluded from the administrative record, my decision of the issues presented would not change.

(A) *Manufacturing Parties' Exceptions.* The manufacturing parties have specifically excepted to certain exclusions of their evidence (Manufacturing Parties' Exemptions, Appendix C). I will, as did the manufacturing parties in their exceptions, review those rulings under the name of the witness, or the number of the exhibit, in question.

Direct testimony of Dr. Booth (M–40). The manufacturing parties except to the striking of a sentence from page 8 of Dr. Booth's testimony. That sentence was stricken neither in the October 20, 1977, order to which they refer nor during cross-examination. Although the sentence referred to appears on its face to be unobjectionable (and I have therefore, considered it), the manufacturing parties' failure to state in what context the decision to strike was made makes reversal of that decision inappropriate.

Direct testimony of Dr. Jensen (M–669). The manufacturing parties except to the exclusion of a statement by Dr. Jensen concerning a study dealing with estrogen receptors. A written report of the study was apparently prepared but not yet published and was not submitted to the record. The data upon which Dr. Jensen based his statements were not available for analysis by the Bureaus, and Dr. Jensen's report of those data is hearsay.

I find, however, that this testimony should have been admitted for what it is worth, and I therefore reverse the Administrative Law Judge's ruling on this issue.

Direct testimony of Dr. Kliman (M–110). The manufacturing parties except to the exclusion from evidence of pages 19 through 29 of Dr. Kliman's testimony. The Bureaus had sought the exclusion on the grounds that this testimony, which dealt specifically with the testimony of Bureaus' witnesses, was argumentative and, in some instances, irrelevant and without factual basis. The statements made in this part of Dr. Kiliman's testimony would more appropriately have been made in a brief. I find, however, that there is sufficient basis for this testimony to support its admission into evidence and I reverse the Administrative Law Judge's ruling with respect to the pages in question. I have discussed Dr. Kilman's testimony, where relevant, above.

Direct testimony of Dr. Tennent (M–132). The manufacturing parties except to the striking of the last sentence on page 7 of Dr. Tennent's testimony. The motion to strike this testimony was originally denied but was then, after cross-examination of Dr. Tennent, granted (Tr. at 1283). The testimony was stricken as hypothetical and not relevant to the proceeding. The statement stricken deals with a calculation for which Dr. Tennent admitted he did not have data (Tr. at 1282) and which was not directly related to the issues at hand. Although it is not clear why there was a need to strike this testimony, I do not find that striking to be error.

The manufacturing parties also except to the striking of a statement by Dr. Tennent concerning a procedure followed by Dr. Williams in attempting to identify radioactivity found in a radioisotope experiment. The first of the two sentences stricken states that Dr. Williams made a certain assumption. The Bureaus moved to strike this statement because Dr. Tennent had not shown a basis for concluding that the assumption had been made. The striking of that sentence appears to have been appropriate. However, the next sentence, which states: "This procedure was counterproductive so far as purification is concerned," is simply a statement of expert opinion on a relevant subject and should not have been stricken. I therefore reverse the Administrative Law Judge's ruling with respect to the latter sentence. I do not, however, consider Dr. Tennent's

testimony to be a basis for discounting the results Dr. Williams reported.

Direct testimony of Dr. C. R. Weaver (M–139). The manufacturing parties object to the striking after cross-examination (Tr. at 1520–21) of a statement by Dr. Weaver about the "apparent experimental design" of the Gass study. Dr. Weaver admitted on cross-examination that he based his testimony on a statement by Dr. Tennent, who was in turn reporting a statement by Dr. Gass (Tr. at 1518). It was within the Administrative Law Judge's discretion to find this double hearsay to be unworthy of admission into evidence in this proceeding, and his ruling is upheld with respect to those statements. The Administrative Law Judge also struck from the record a statement by Dr. Weaver about the usual procedure in a controlled experiment. This testimony is relevant only if Dr. Weaver's hearsay testimony about the experimental design of the Gass study remains in the record. Thus, the striking of this testimony was also appropriate.

The manufacturing parties object to the striking of two paragraphs (at pages 19 and 20 of M–139) that seek to incorporate the views of a Professor Mantel. I believe that a fairly liberal policy with respect to the receipt of hearsay is appropriate in a proceeding such as this one. One legitimate function of that rule, however, is to force the parties to present witnesses that they regard as important for cross-examination. If the manufacturing parties wished to rely upon the views of Professor Mantel, they had an obligation to present him as a witness for cross-examination. This testimony was properly stricken as hearsay.

Exhibits M–141 and M–142. The manufacturing parties object to the exclusion from evidence of affidavits of Drs. Nathan Mantel and David Salsburg. Because neither of these individuals was made available for cross-examination, the striking of their affidavits was entirely justified. (Although the manufacturing parties argue that this ruling by the Administrative Law Judge is inconsistent with other rulings that permitted witnesses to refer to statements of other experts, they provide no examples of such "other rulings.")

Exhibit M–148a. This exhibit purports to list reported residue findings for animal drugs other than DES. The striking of this exhibit is consistent with the agency's, and the Administrative Law Judge's, established position that an administrative hearing on one product is not a proper forum for an argument that that product is being treated differently than other products. This position has been recently upheld by the United States Court of Appeals for the District of Columbia Circuit, *Edison Pharmaceutical Co., Inc.* v. *FDA*, No. 77–1636, slip op. at 23 (D.C. Cir. March 21, 1979).

In any case, as discussed in section III(B)(3) of this Decision, the evidence with respect to the regulatory treatment of the residues of other drugs is irrelevant to the evidence with respect to DES because the residue findings are not comparable. With respect to other drugs, residues should be detectable by the approved methods at any level above a computed "safe" or "virtually safe" ("no residue") dosage. Since no "safe" or "virtually safe" dosage for DES can be ascertained, there is no evidence of the number of residues existing in edible meat products above that dosage level for DES. Certainly the Department of Agriculture findings, which at best provide evidence of the number of residues above 0.5 ppb DES, are not comparable to the residue figures for other drugs.

Surrebuttal testimony of Dr. Jensen (M–203) and referenced papers (M–204–208). Briefs to the Administrative Law Judge were due to be filed on March 30, 1978. On March 3, 1978, the manufacturing parties presented the purported surrebuttal testimony of Dr. Jensen together with a number of papers that had not yet been made part of the administrative record. The Administrative Law Judge reviewed this new evidence and concluded correctly that it was not proper surrebuttal. The arguments made by Dr. Jensen, in almost all instances, would more appropriately have been made in the final brief of the parties. In fact, Dr. Jensen's testimony has been included in the manufacturing parties' brief (Manufacturing Parties' Exceptions, Appendix B).

The Administrative Law Judge's decision to exclude this evidence on the ground that it was not proper surrebuttal was correct. Surrebuttal is justified only by a showing of the necessity to respond to unanticipated issues raised during rebuttal. It is clearly not appropriate for the manufacturing parties to seek to introduce as surrebuttal new evidence that could have been produced earlier in the hearing and would have been subjected to the scrutiny of the witnesses for all parties. Since there was no showing that exhibits M–204–208 were not available earlier in the proceeding (or that the issues to which they are relevant were not raised earlier in the proceeding); the Administrative Law Judge's decision with respect to these documents was clearly justified.

The manufacturing parties' desire to have the last word (and perhaps to delay the completion of the hearing, since acceptance of surrebuttal testimony would have led to further cross-examination) is understandable. Administrative hearings have to end sometime, however, and the conclusion of this hearing prior to the submission of the manufacturing parties' purported surrebuttal evidence was appropriate.

Exhibit M–209. As discussed below, the Administrative Law Judge allowed the Bureaus to submit into evidence an interim report (G–192) of the "Chicago study", discussed above (see section III(D)(2)(b) above). In their opposition to admission of this document, the manufacturing parties submitted a statement by Dr. Herbst, who had been a witness for the Bureaus. Dr. Herbst, in this statement, gave his opinion that the report was not evidence of carcinogenicity of DES in humans. The exhibit (G–192) was nevertheless admitted and, on March 20, 1978, (ten days before final briefs were due), the manufacturing parties moved Dr. Herbst's statement into evidence (Record No. 373). On March 24, the Administrative Law Judge denied the motion for admission of Dr. Herbst's statement.

Exhibit G–192 was an update of a study about which all parties had had an opportunity to comment. Neither the Bureaus nor the manufacturing parties were given an opportunity to present testimony concerning the update. Accepting testimony from either side on this report would have required another round of cross-examination.

The Administrative Law Judge noted that, by the terms of Dr. Herbst's statement, Dr. Herbst and the other researchers working on the "Chicago study" had completed an analysis of the study. They were not, however, willing to submit that analysis to the administrative record before the publication of the analysis in April. The failure to admit, at that late date in the proceeding, the partial, conclusory evaluation of the study that was proffered is not error. The manufacturing parties were free to comment upon the information presented by the report and have done so in their briefs. (As noted above, I have considered Dr. Herbst's statement in any case.)

The manufacturing parties also objected to the admission into evidence of certain testimony and exhibits presented by the Bureaus.

Direct testimony of Dr. Bixler (G–11). One sentence from this testimony is objected to because it uses the phrase "the livestock producer may think he is

feeding his animals a withdrawal (nonmedicated) feed" (G–11 at 2). The manufacturing parties argue that this testimony "purports to probe the mental processes of 'the livestock producer,'" (Manufacturing Parties' Exceptions, Appendix C at 13). Since the rest of this statement explains Dr. Bixler's view of the likelihood of unintentional DES drug carryover, this testimony is properly admissible. I have not, however, relied upon Dr. Bixler's testimony in this Decision.

Cross-examination of Dr. Bixler. The manufacturing parties object to a statement made by Dr. Bixler on cross-examination in which he testified that it was possible that animals implanted with DES might also be inadvertently fed feed containing DES. The Administrative Law Judge correctly denied a motion to strike this statement; he thought the question on cross-examination was unnecessary and that the answer was obvious. He noted that counsel for the manufacturing parties had, in his objection to the question, pointed out that anything was possible.

Dr. Bixler also stated that "farmers have admitted that they have fed DES feed in conjunction with implanting" (Tr. at 571). This statement is hereby stricken as hearsay.

Exhibit G–47. The manufacturing parties move to strike this document, entitled "Survey of Compounds Which Have Been Tested for Carcinogenic Activity." This is a government publication briefly summarizing test results with respect to the carcinogenic activity of various substances. An administrative law judge is not bound by the Federal Rules of Evidence, though Judge Davidson sought to apply them to the extent reasonable in this proceeding. The Administrative Law Judge concluded that G–47 was admissible, even though hearsay, either because it was a public record or report or because its admission otherwise served the purposes of justice; see Rule 803, Fed. R. Evid.

The admission of this exhibit might conceivably have been improper if it had been intended to show the results of a particular study about which there was an active dispute and if that study had not been produced. Here, however, that was not the case. The studies specifically relied upon by the Bureaus were produced. This exhibit was proffered merely to demonstrate that DES is carcinogenic. The Administrative Law Judge's decision not to strike this document was proper. There is sufficient evidence in the record showing DES to be a carcinogen in animals so that, if G–47 had been excluded from evidence, my findings would not change on any issue.

Direct testimony of Dr. Highman (G–54). The manufacturing parties object to the entire direct testimony of Dr. Highman. Dr. Highman reported on incomplete results of the NCTR DES animal study. The manufacturing parties also submitted testimony with respect to incomplete reports of the results of this study (see section III(D)(2)(a) of this Decision). The question of how to deal with ongoing studies in an administrative hearing is a difficult one. I have concluded that it is not appropriate to rely, in an administrative hearing, upon incomplete reports of results of a study of this type. Although the technical question of whether this testimony is admissible is perhaps a close one, in light of the fact that I have assigned no weight to this evidence (see section III(D)(2)(a) of this Decision), I hold that this testimony should be excluded.

Direct testimony of Dr. Kokoski (G–57). The manufacturing parties seek to strike certain testimony of Dr. Kokoski setting out what he and the Bureau of Foods' Division of Toxicology consider necessary to show the safety of a substance. The manufacturing parties' objection to this testimony is that it represents the views not of the individual witness but of the division of the Bureau. Since, however, Dr. Kokoski stated that this testimony on these subjects was in fact a statement of the criteria he would use in evaluating the safety of a substance (Tr. at 1018–19), it is apparent that this testimony is properly admissible. I conclude that the exclusion of his testimony on this subject would not have led me to a different decision with respect to the safety of DES.

Cross-examination of Dr. Kokoski. The manufacturing parties refer to a response to a question asked Dr. Kokoski on cross-examination in which Dr. Kokoski stated his opinion that the "law does not provide for establishing a safe tolerance for an agent which is shown to induce cancer" (Tr. at 1045). The manufacturing parties moved to strike this sentence, apparently on the grounds, urged at the time of cross-examination, that Dr. Kokoski is not qualified to give an opinion on a legal question. I fail to see why any time is wasted by either making this objection or appealing the ruling denying it. It would seem an obvious matter that Dr. Kokoski's opinion on a legal matter will be given no weight. Because the legal opinion was not within Dr. Kokoski's expertise, however, the Administrative Law Judge's ruling on this issue is reversed.

The manufacturing parties also object to three answers by Dr. Kokoski to questions on redirect examination (Tr. at 10, 48–49). In this testimony Dr. Kokoski stated that Exhibit G–24 refers to drugs in general, though its primary thrust deals with carcinogenic drugs. The manufacturing parties then moved to strike this redirect examination as not having been covered on cross-examination. The Administrative Law Judge denied the motion to strike on the ground that whether or not the witness was correct in his appraisal of the exhibit was immaterial, because the exhibit was in evidence (and could thus be evaluated on its own merits). He stated, "I do not know what you are fussing about" (Tr. at 1049). I concur in the Administrative Law Judge's comment upon the frivolousness of this motion. It is unclear whether the Administrative Law Judge ruled upon the issue of whether the testimony in question was proper redirect examination. As I can find nothing in the cross-examination of Dr. Kokoski that deals with the subject of his redirect, I must reverse the Administrative Law Judge's denial of this motion.

Direct testimony of Dr. Levy (G–58). The manufacturing parties ask that this entire testimony be stricken because Dr. Levy did not have personal knowledge of the factual data upon which he based his statistical calculations (discussed above in section III(B)(3) of this Decision). Dr. Levy's testimony can be accepted, at the very least, as demonstrating the fact that a relatively small number of detected residues represent a larger number of residues among all animals treated. (The manufacturing parties do not object to this treatment of the testimony, Tr. at 738.)

Dr. Levy testified that the figures he utilized in this testimony were government figures provided by the United States Department of Agriculture. The manufacturing parties provided no basis for suspicion that these figures are not correct. In an administrative hearing of this type, struct adherence to the evidentiary rules of courtrooms is neither required nor efficient. If there were any reason to believe that USDA had in fact not found the residues reported by Dr. Levy or if the difference of a few residue detections more or less would make a difference in my ultimate decision, there would be more reason to require technical proof that the figures to which Dr. Levy testified were correct. Because neither of these reasons, nor any other reason of which I am aware, requires

dismissal of Dr. Levy's testimony, I have relied upon it and hold that the denial of the motion to strike this testimony was appropriate.

I have considered whether exclusion of Dr. Levy's testimony would require reversal of any of my findings in this proceeding. FDA Establishment Investigation Reports have been submitted to the record (as G–89) that show FDA investigations of USDA DES residue findings (see also G–139, G–140). Thus, there would be evidence of such findings—upon which I would base the conclusion that USDA findings show that DES use results in DES residues in edible tissues—even were Dr. Levy's testimony excluded.

Direct testimony of Dr. Rodricks (G–72). The manufacturing parties move to strike Dr. Rodricks' statement that, because the USDA monitoring program was utilizing a method with a lowest level of measurement above the level that would be considered adequate for DES, it must be concluded that a far higher residue occurrence rate would be observed if a method with a lower level of measurement were utilized by the monitoring program (G–72 at 6). The manufacturing parties argue that this conclusion is speculative and without factual basis in the record. However, Dr. Rodricks was an expert witness, and the conclusion is appropriately based upon his expertise. (Indeed, the conclusion he voiced is self-evident to one with basic scientific knowledge about the occurrence of residues.)

The manufacturing parties also object to the admission into evidence of a number of statements by Dr. Rodricks (id. at 7–10) that they consider to be "argumentative, hearsay, and to a large extent not based upon evidence of record." I have reviewed the statements objected to and find the manufacturing parties' objections to them to be unfounded.

Direct testimony of Dr. Saffiotti (G–80). The manufacturing parties move to strike the first seven pages of Dr. Saffiotti's eight page written direct testimony on the grounds that it set out procedures for determining whether chemical carcinogens are safe and that Dr. Saffiotti was unable to relate DES to chemical carcinogens. The manufacturing parties' argument is that DES is simply another estrogen and thus not a chemical carcinogen. As discussed in some detail above (section III(D)(1)), I find that DES is not simply another estrogen and may have some properties of chemical carcinogens. Thus, Dr. Saffiotti's testimony is relevant to DES, and the refusal to strike this testimony was justified. (The first one and one quarter pages of the testimony contains, at any rate, a description of Dr. Saffiotti's qualifications and would not, even if the manufacturing parties' theory had validity, be stricken.)

The manufacturing parties also object to a statement by Dr. Saffiotti that: "It is clear that DES is a cancer-causing agent in animals and in humans," and to a subsequent statement that a publication containing summaries of experimental and epidemiological data supports that statement (G–80 at 7). The manufacturing parties argue that they were unable to cross-examine Dr. Saffiotti fairly on his conclusion that DES is a cancer-causing agent because they had not been provided with copies of all of the reports summarized in the publication referred to. However, Dr. Saffiotti's expertise in this area is clear (G–80 at 1–2; G–80a; G–80b), and he is qualified to give the opinion, based upon literature upon which he reasonably relies in forming opinions of this type, that DES is a carcinogen (cf. Rule 703, Fed. R. Evid.; *McCormick on Evidence* (2d Ed. 1972) at 36). Thus, his conclusion on that point would be admissible whether or not he had stated that data supporting his testimony were summarized anywhere.

The statement that such summaries exist seems to be straightforward and need not be stricken. A study in the record showing DES to be a carcinogen, such as the Gass study, is, of course, given more weight than the statement of an expert, unsupported by submitted evidence, that DES is a cancer-causing agent. The latter statement is, however, relevant evidence and should be considered as such (id.). I note that there is ample evidence of the carcinogenicity of DES in the record so that, if Dr. Saffiotti's testimony were excluded, no finding I have made in this proceeding would change.

Exhibits G–139 and G–140. These exhibits contained reports from the Department of Agriculture to the FDA about recent findings of DES residues. It was established on the record that these memoranda were prepared and transmitted in the normal course of government business (Tr. at 1183–84). As such, these documents are properly admissible in a Food and Drug Administration administrative hearing. Even if they did not, as they appear to do, come within a recognized exception to the Federal Rules of Evidence hearsay rule, Rule 803(8)(B), Fed. R. Evid., it would be necessary for the orderly conduct of Food and Drug Administration administrative hearings to admit this type of evidence unless a reasonable basis for believing that the evidence was not correct had been proffered. No such basis was proffered here. I note that these documents were only cumulative of other evidence of USDA residue findings and that exclusion of them would not, therefore, change my finding on any issue.

Direct testimony of Dr. Shimkin (G–90). The manufacturing parties object to the testimony by Dr. Shimkin to the effect that it is not possible to conclude that any level of DES residues can be shown to be safe for human consumption. Though the manufacturing parties argue that this is a legal conclusion, I do not share that characterization. The statement objected to is an appropriate conclusion for an expert witness. Even under the Federal Rules of Evidence, an expert witness may give his opinion on the ultimate issue to be decided by the factfinder. Rule 704, Fed. R. Evid. This testimony is not, however, an essential basis for any finding that I have made.

Direct testimony of Ms. Weissinger (G–95). The manufacturing parties object to testimony by Ms. Weissinger about a study of the breakdown of DES conjugates in humans. This study was an outgrowth of work she had done on the subject in animals (see G–95; Tr. at 827–28). Ms. Weissinger was not a party to the actual performance of the tests in humans. The manufacturing parties object to her testimony about the study on that ground. However, the record is replete with testimony by persons shown to have expertise about studies that they did not perform (see, for example, my discussion of the conflicting expert interpretations of the Gass study in section III(D)(2)(a)). Ms. Weissinger has significant expertise in the performance and evaluation of this general type of study (G–95 at 1–2; G–95a), and there is thus no valid objection to her testimony concerning this study, a report of which is part of the record (G–97). Because the study itself was part of the record of this proceeding, I find that I would reach the same conclusions about the significance of this study even were Ms. Weissinger's testimony excluded.

Submission of Dr. Williams (G–102). The manufacturing parties object to Dr. Williams' statement that "[t]here appears to be no reasonable doubt that DES conjugate(s) are present in liver 120 days after implantation of ^{14}C–DES" (G–102: Comments on the Vineland Laboratories Submission at 1). The manufacturing parties' objection to this statement as being beyond the expertise of the witness, speculation and without proper foundation, is totally without merit. Dr. Williams has been shown to be an expert in this area (G–99 at 1; G–

99a; G–99b). A second sentence in the same paragraph, in which Dr. Williams gives his opinion as to whether a conjugate constitutes a residue of DES, is less clearly within Dr. Williams' area of expertise. The question is simply one of semantics. Whether or not conjugates found in animal tissues as the result of the use of DES are characterized as "residues" is of no significance in this hearing. Although I have not relied upon Dr. Williams' testimony on this issue, I conclude that the Administrative Law Judge's refusal to strike it was proper.

The manufacturing parties object to a statement by Dr. Williams that an estrogen conjugate is known to give rise to high circulating plasma levels of free estrogen in humans after oral administration. Dr. Williams cited a private communication from another scientist for this proposition (G–102: Comments on the Vineland Laboratories Submission at 2). The manufacturing parties were not given an opportunity to examine the data (or a report of the study) about which Dr. Williams testified, and Dr. Williams' statement is hearsay. I have concluded, however, that this statement like that of Dr. Jensen in M–69, discussed at the beginning of this section, should have been admitted for what it was worth. I have, however, not relied upon this statement.

The manufacturing parties also object to a further statement by Dr. Williams that he feels that "it is most probable that conjugated DES occurring in animal tissues will give rise to free DES after ingestion by humans" (id.). Contrary to the manufacturing parties' assertion, this statement is not beyond the expertise of the witness, does not constitute hearsay, and is an appropriate expression of an expert's opinion. (Dr. Williams cited bases for this opinion other than the hearsay statement discussed above (id.). In any case, that information would be a permissible basis for the formation of his opinion, rule 703, Fed. R. Evid.) Even were Dr. Williams' testimony excluded, other evidence in the record (see section III(C) of this Decision) would support the conclusion, discussed above, that I have drawn on this issue.

Exhibit G–137. The manufacturing parties object to the admission of this summary of the results of FDA investigations of DES residues. Apparently the manufacturing parties at one time thought this document was admissible, as they submitted it themselves (M–27). Nevertheless, there does not appear to be a clear explanation in the record of how this document was prepared. Nor is there any clear showing that this is a document prepared in the normal course of government business, though its format would suggest that it is. If the document summarized only establishment inspection reports that were submitted to the record, it might be admissible as a shorthand summary of those documents. However, some of the establishment inspection reports noted in the summary were not provided to the record. It appears that this document should have been stricken from evidence and I reverse the Administrative Law Judge's decision not to strike this document. I have disregarded the document in reaching my decision.

Exhibit G–192. This exhibit is the interim report of the Chicago study discussed above. The manufacturing parties' basic objection to this document is that it was submitted after the hearing was, in effect, completed and that the manufacturing parties were not provided a chance to present testimony analyzing the document. The Bureaus were not, however, given an opportunity to present testimony analyzing this document either. The manufacturing parties treat this document as if it were testimony as to which rebuttal evidence would be proper. The document, however, constitutes only data from which all parties can draw whatever conclusions appear to be appropriate.

Since this document was not available prior to the hearing itself, its admission after it became available was proper. Because I have based no conclusions on this document—see, e.g., discussion of human carcinogenicity data in section III(D)(2)(b)—the manufacturing parties are not, in any case, prejudiced by its admission.

(B) Bureaus' Exceptions

The Bureaus except only to the exclusion from evidence of certain statements that they regard as the opinions of experts on ultimate issues. Although I have not relied on any such statements, I regard the exclusion of expert testimony on the ground that it involves an opinion on the ultimate issue as inappropriate. The common law rule against such testimony was designed to protect fact-finding juries. Certainly here neither the Administrative Law Judge nor I am likely to be unduly swayed by any expert's opinion on an ultimate issue. The common law rule has, in any case, been changed for federal courts, Rule 704, Fed. R. Evid.

VII. Effective Date

The risk associated with continued use of the DES animal drugs is, though unquantifiable, significant. For that reason I do not believe that a substantial delay of the effective date of my decision is appropriate. Certainly no such delay would be proper without a clear showing that an early effective date would cause economic disruption in the meat production industry.

It is also true, however, that in a complex set of activities such as the manufacture, shipment, and use of animal drugs involving many economic units in different parts of the country, it is not feasible to terminate operations with a widely used drug immediately. Moreover, although for several years there have been clear signals that the continued approval of DES was in jeopardy (particularly, the Administrative Law Judge's decision in September, 1978), nevertheless there are legitimate reliance interests on the part of animal producers who, during the period while DES was approved, have administered it to animals that they will be bringing to slaughter in coming months. Those reliance interests deserve some equitable consideration.

I have concluded, therefore, that this decision will become effective in 14 days (on July 13, 1979) with respect to the manufacture of DES animal drugs and the shipment of DES animal drugs by anyone (including manufacturers, wholesalers, jobbers, and other middlemen or persons acting as middlemen). That effective date is intended to allow a fair and reasonable period (but no more than a fair and reasonable period) to bring the production and shipment of these products to an end. Petitions for stay of this effective date may be submitted pursuant to 21 CFR 12.139, 10.35; and arguments contained in such petitions will be considered expeditiously. Submission of such petitions will not, however, automatically stay this effective date.

I am also delaying the effective date of this action 21 days (until July 20, 1979) with respect to the administration of DES animal drugs to animals (in any form whether as an additive to feed or as an implant) and the manufacture, shipment, and use of feed containing DES. This effective date is intended to allow a fair and reasonable period (but not more than a fair and reasonable period) to bring these activities to an end. A somewhat longer period is allowed for bringing these activities to an end than is being allowed to terminate the manufacture and shipment of DES drugs. The reason for this difference is that the activities relating to the use of DES in feed or in animals involve many more economic units, some of which are small and may not

learn of this decision immediately. I have set this second effective date in the expectation that a petition or petitions for stay of this action will be received by the FDA prior to the end of the 21 day period. See 21 CFR 12.139; 10.35. Receipt of such petitions will automatically stay the effect of this decision with respect to the activities and persons covered by this paragraph for another period of 14 days (August 3, 1979). If petitions are received within 21 days, either they will be ruled upon before the end of the additional 14 day period or that period will be extended pending a ruling on the request for stay. I recognize that 21 days is a relatively short time within which to prepare the necessary papers. I also believe, however, that it is sufficient time; and I am concerned about the risk to the public from any continued use of DES animal drugs.

This Decision will not be effective with respect to edible products of animals treated with DES animal drugs when the treatment of the animals was before the effective date for use of the drug. Any added treatment of such animals with DES after the effective date (including the continuation of feeding with DES-treated feed begun before the effective date) will, however, make the meat from the treated animals adulterated within the meaning of the Federal Food, Drug, and Cosmetic Act; see discussion below. Implants inserted before the effective date will not be effected by this Decision even if they continue to operate after the effective date; no new or additional implants may be inserted, however, after the effective date.

I will first describe the legal consequences that will flow from my decision to withdraw approval of these NADA's on the dates that this decision becomes effective. I will then discuss the options that may be available to the agency if it finds that any further stay is appropriate. Finally, I will outline the data that must be submitted to support any petition for a further stay of this action.

The animal drugs themselves will, upon withdrawal of approval of the NADA's that cover them, be deemed, pursuant to 21 U.S.C. 360b(a), to be "unsafe" within the meaning of 21 U.S.C. 351(a)(5). Thus, pursuant to the latter section, these drugs will be "adulterated".

The withdrawal of approval of the NADA's will also mean that, pursuant to 21 U.S.C. 360b(a), DES will be deemed unsafe within the meaning of 21 U.S.C. 342(a)(2)(D). Pursuant to the latter section, any food containing DES will be deemed adulterated. Thus, animal feed containing DES and the edible products of animals treated with DES will be adulterated food within the meaning of the Federal Food, Drug, and Cosmetic Act.

The following acts with respect to adulterated drugs and adulterated foods (and thus with respect to DES, animal feed containing DES, and edible products of animals that have been treated with DES) are violations of federal law:

1. The act of, or causing the act of, the introduction or delivery for introduction into interstate commerce of such drugs or foods, 21 U.S.C. 331(a).
2. The act of, or causing the act of, receipt in interstate commerce of such drugs or foods or the delivery or proffered delivery of such drugs or foods, 21 U.S.C. 331(c).
3. The act of, or causing the act of, manufacture of such drugs or foods within the District of Columbia or any other federal territory, 21 U.S.C. 331(g).
4. The manufacture or doing of any other act with respect to a product if that act is done while the product is held for sale after shipment in interstate commerce and results in the adulteration of the product, 21 U.S.C. 331(k).

I interpret the latter provision as prohibiting the manufacture of DES, the mixing of DES with feed, and the treating of animals intended for food with DES when either the DES, its components, the feed, or the animals involved have crossed a state line.

If the FDA finds that a further stay of the effective date of this action is appropriate, several options suggest themselves. The decision might be stayed until judicial review of it has been completed. I do not regard that possibility as likely. The risk of use of DES is significant, and I believe that my decision is correct and will be upheld.

The agency could allow all existing stocks of DES to be used up. Alternatively, the agency could allow all existing stocks held by cattle producers and feed lots to be used up, but refuse to stay this decision as to stocks of DES that are now held by manufacturers or middlemen. Another alternative would be to stay the decision with respect to feed with which DES has already been mixed, but to deny a stay as to unused DES implants and DES drugs not yet mixed with feed.

I do not believe that I can make a decision adopting any of the alternatives listed without knowledge of how much DES is not available on the market, in what forms, and in whose hands that DES is. Cf. *Environmental Defense Fund, Inc.* v. *Environmental Protection Agency*, 510 F.2d 1292, 1306 (D.C. Cir. 1975).

Petitions for stay of the effective date of my decision should be submitted in the format prescribed by 21 CFR 10.35. They should identify the type of stay requested. The agency has no intention of allowing existing stocks of DES to be used up if it is apparent that manufacturers, cattle producers, or others have been stockpiling unusually large quantities of DES against just such a decision. The following information should be submitted in support of any petition:

1. The amount of existing stocks of DES held by manufacturing parties;
2. The amount of existing stocks of DES held by cattle producers and feed lots;
3. The amount of existing stocks of DES held by middle men, carriers, and other persons.
4. The time that it is estimated would be required to use up any presently existing stocks of DES (a) held by manufacturing parties, and (b) held by others.
5. A comparison of the amount of DES produced from January 1 through June 30, 1979, with the amount produced during the comparable period in 1976, 1977 and 1978.
6. A statement of the amount of DES produced between June 29, 1974, and July 13, 1979 (the effective date of this decision with respect to manufacture of DES animal drugs).
7. An explanation of the petitioner's reasons for believing that a stay would cause economic disruption in the cattle producing industries, accompanied by factual data supporting that explanation.
8. An explanation of the legal basis upon which the petitioner relies in requesting the type of stay requested.
9. Any other reason that the petitioner believes justifies a total or partial stay of this decision.

The petition for stay should be accompanied by sworn statements by the responsible individuals within the firms in question (manufacturing parties, middlemen, and the larger cattle producers and feed lots) as to the existing stocks of DES. The agency will entertain requests that information regarded as trade secret be kept confidential. See 21 CFR 10.20(i); 514.11(g)(2). The FDA will discount statements that are not sworn. Due to its concern about the possibility of stockpiling, I am announcing now that the FDA will presume that the failure to submit information about the existence of stocks in any major component of the stream of commerce for DES means that large stocks are held by that component.

I should note with respect to the question of the effective date that I reject the argument that, because it has taken the FDA several years to issue a final decision with respect to the DES animal drugs, that decision can be delayed yet a longer time. The delay in the issuance of this decision reflects the importance of the decision and the fact that administrative hearings on complicated issues simply take a long

time. The case of DES itself demonstrates the results of attempts by the agency to utilize procedural shortcuts. (As discussed in section I of this Decision, the previous withdrawal of approval of these NADA's was overturned on judicial review.) Thus, in the absence of a clear showing that, in accordance with the dates announced above, the implementation of this decision will seriously disrupt the meat production industry, the FDA intends to make this decision effective on these dates.

VIII. Conclusion

My conclusions with respect to the various issues in this hearing, together with citations to the record in support of my conclusions, have been stated as part of my discussion of those issues. The following is a summary of those conclusions:

1. Neither the mouse uterine/paper chromatography method, which is the currently approved method, nor any other analytical method has been shown to be acceptable to be approved or to remain approved for purposes of the so-called "DES exception" to the "Delaney Clause," 21 U.S.C. 360b(d)(1)(H).

2. DES is a carcinogen when ingested by animals. Evidence in the record suggests that DES is a carcinogen when ingested by human beings. There is no known no-effect level for the carcinogenic properties of DES.

3. Because I have revoked approval of the analytical method for detecting DES residues and have not substituted for it any other approved method, DES cannot qualify for the "DES exception" to the "Delaney Clause." The Delaney Clause, therefore, applies to DES and, because DES has been found to induce cancer in animals, requires withdrawal of approval of all DES NADA's 21 U.S.C. 360b(3)(1)(B); (d)(1)(H).

4. DES has adverse biological effects other than carcinogenesis, specifically teratogenic and mutagenic effects, which raise serious questions about its safety. On the record in this proceeding, those questions have not been resolved. No safe tolerance levels can be established for these effects.

5. The record demonstrates that use of DES animal drugs pursuant to their approved conditions of use (and, with respect to DES used in animal feed, use with a 14-day withdrawal period) results in residues of DES in the edible tissues of treated animals after slaughter. Although it is impossible to tell at what level these residues appear, residues will result at levels that must be regarded as significant from a public health standpoint. There has been no showing that any level of DES residue in edible tissues of treated animals is safe.

6. The Bureaus have provided new evidence that, together with evidence previously available, shows that the DES animal drugs are not shown to be safe for use under the conditions of use upon the basis of which the DES NADA's were approved. Approval of those NADA's must, therefore, be withdrawn pursuant to 21 U.S.C. 360b(e)(1)(B).

7. FDA is not authorized, under the Food, Drug and Cosmetic Act, in considering the question whether a new animal drug has been shown to be safe for use, to weigh the "socio-economic" benefits that that drug provides against a health risk to the ultimate human consumers of treated animals. Even were I to attempt to weigh the benefits of DES against its risks, this record would not provide sufficient information to compute the risk associated with DES or to determine whether, and to what extent, use of DES provides any health benefit or even any economic benefit to society.

8. This record provides no evidence upon the basis of which I can conclude that there are any conditions of use of the DES animal drugs under which use of those drugs would be shown to be safe. The discard of all livers (or any other organs) of these animals would not constitute a condition of use that has been shown to be safe.

9. Because alternatives to DES are available, I conclude that the withdrawal of approval of these NADAs will not significantly affect the quality of the human environment.

Dated: June 29, 1979.

Donald Kennedy,

Commissioner of Food and Drugs.

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